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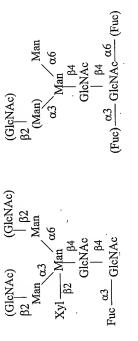
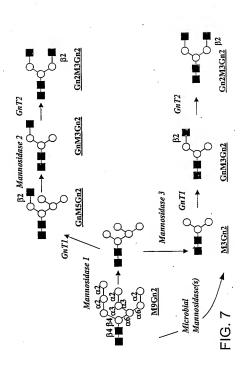
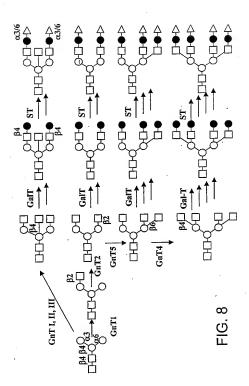
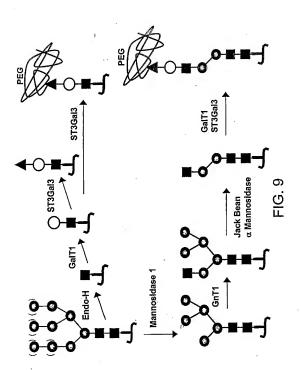


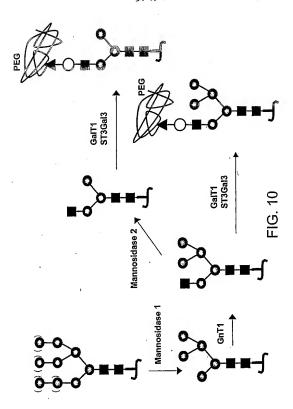
FIG. 6



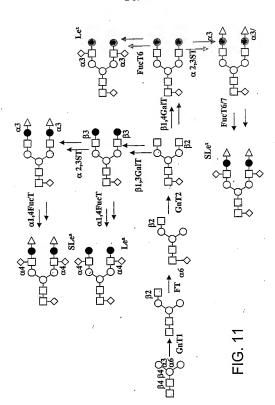
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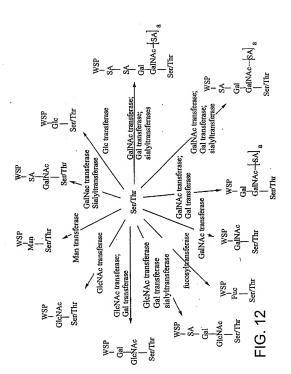






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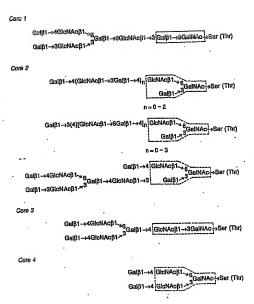
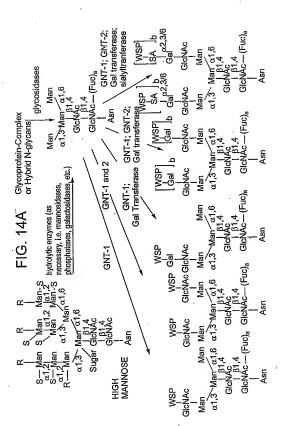
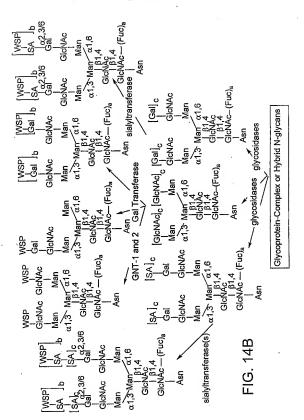


FIG. 13





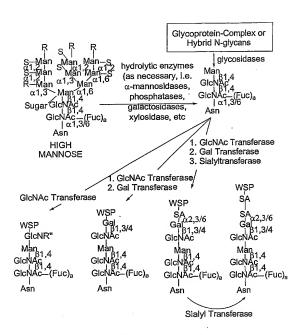


FIG. 15

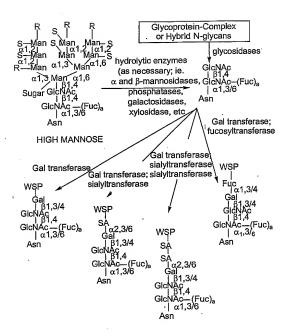


FIG. 16

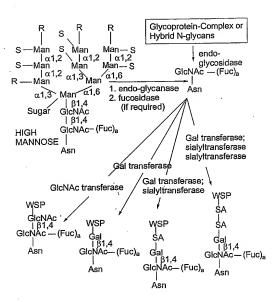
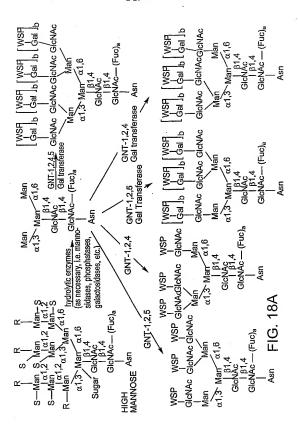
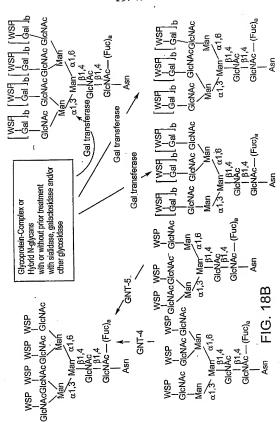
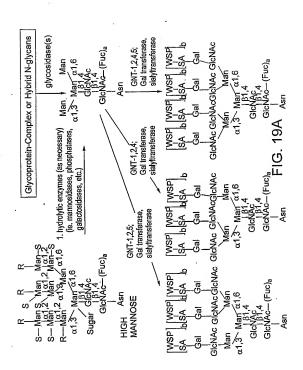
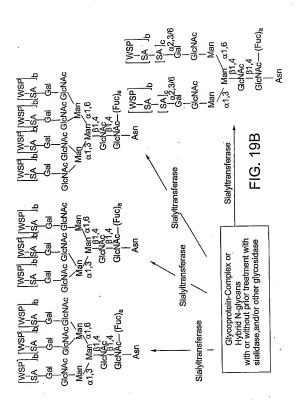


FIG. 17









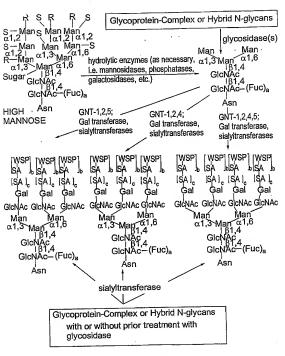
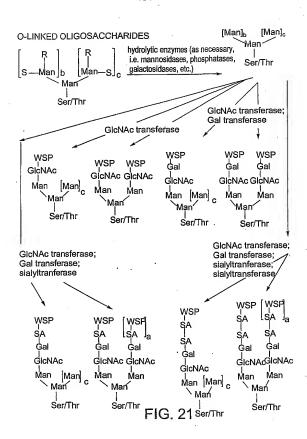
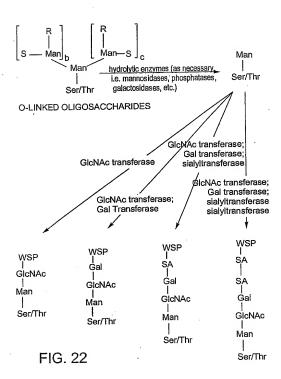
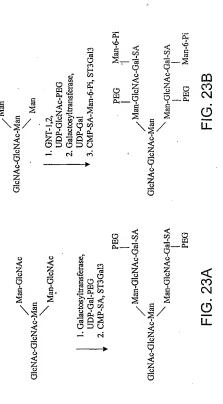


FIG. 20







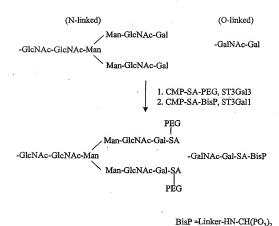


FIG. 23C

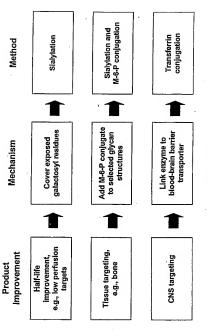


FIG. 24

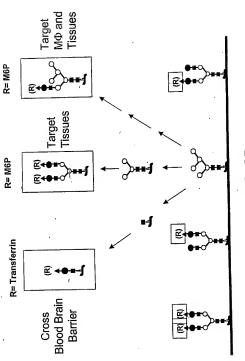
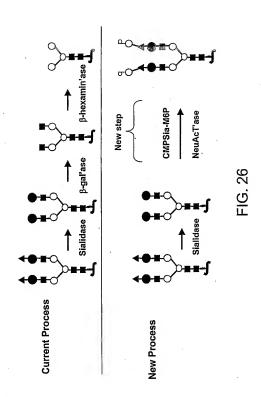
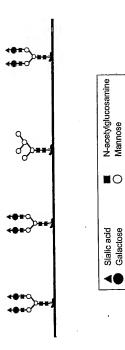


FIG. 25





=1G. 27

12AP1/F5 -- Viventia Biotech 1964 - Aventis 20K growth hormone -- AMUR 28P6/E6 -- Viventia Biotech 3-Hydroxyphthaloyl-beta-lactoglobulin -4-IBB ligand gene therapy -64-Cu MAb conjugate TETA-1A3 --Mallinckrodt Institute of Radiology 64-Cu MAb conjugate TETA-cT84.66 64-Cu Trastuzumab TETA conjugate -Genentech A 200 -- Amgen A10255 - Eli Liliv A1PDX - Hedral Therapeutics A6 -- Anastrom aaAT-III -- Genzyme Abciximab - Centocor ARI 001 - Atlantic BioPharmaceuticals ABT-828 - Abbott Accutin Actinohivin activin - Biotech Australia, Human Therapeutics, Curis AD 439 - Tanox AD 519 - Tanox Adalimumab -- Cambridge Antibody Tech. Adenocarcinoma vaccine - Biomira - NIS Adenosine deanimase -- Enzond Adenosine A2B receptor antagonists --Adenosine Therapeutics ADP-001 - Axis Genetics AF 13948 - Affymax Afelimomab - Knoll AFP-SCAN - Immunomedics AG 2195 - Corixa agalsidase alfa -- Transkaryotic Therapies agalsidase beta - Genzyme AGENT- Antisoma Al 300 - Autoimmune Al-101 - Teva Al-102 - Teva

Al-201 - Autolmmune AI-301 - AutoImmune AIDS vaccine - ANRS, CIBG, Hesed Biomed, Hollis-Eden, Rome, United Biomedical, American Home Products, Maxvoen airway receptor ligand - IC Innovations AJvW 2 - Ajinomoto AK 30 NGF -- Alkermes Albuferon -- Human Genome Sciences albumin - Biogen, DSM Anti-Infectives. Genzyme Transgenics, PPL Therapeutics, TranXenoGen, Welfide Corp. aldesleukin -- Chiron alefacept -- Biogen Alemtuzumab Allergy therapy -- ALK-Abello/Maxygen, Al K-Abello/RP Scherer allergy vaccines -- Allergy Therapeutics Alnidofibatide - Aventis Pasteur Alnorine -- SRC VB VECTOR ALP 242 -- Gruenenthal Alpha antitrypsin -- Arriva/Hyland Immuno/ProMetic/Protease Sciences Alpha-1 antitrypsin - Cutter, Bayer, PPL Therapeutics, Profile, ZymoGenetics, Arriva Alpha-1 protease inhibitor -- Genzyme Transgenics, Welfide Corp. Alpha-galactose fusion protein -**Immunomedics** Alpha-galactosidase A - Research Corporation Technologies, Genzyme Alpha-glucosidase - Genzyme, Novazyme Alpha-lactalbumin Alpha-L-iduronidase - Transkaryotic Therapies, BioMarin alteplase - Genentech alvircept sudotox -- NIH ALX1-11 -sNPS Pharmaceuticals Alzheimer's disease gene therapy

FIG. 28A

Anti-angiogenesis monoclonal antibodies --AM-133 -- AMRAD KS Biomedix/Schering AG Amb a 1 immunostim conj. - Dynavax Anti-B4 MAb-DC1 conjugate -- ImmunoGen AMD 3100 ~ AnorMED ~ NIS AMD 3465 - AnorMED - NIS Anti-B7 antibody PRIMATIZED - IDEC AMD 3465 - AnorMED - NIS Anti-B7-1 MAb 16-10A1 AMD Fab -- Genentech Anti-B7-1 MAb 1G10 Amediplase - Menarini, Novartis Anti-B7-2 MAb GL-1 AM-F9 Anti-B7-2-gelonin immunotoxin -Antibacterials/antifungals --Amoebiasis vaccine Diversa/IntraBiotics Amphiregulin - Octagene Anti-beta-amyloid monoclonal antibodies -anakinra - Amgen Cambridge Antibody Tech., Wyeth-Ayerst analgesic -- Nobex Anti-BLvS antibodies -- Cambridge ancestim - Amgen Antibody Tech. /Human Genome Sciences AnergiX.RA - Corixa, Organon Antibody-drug conjugates -- Seattle Angiocidin - InKine Genetics/Eos angiogenesis inhibitors -- ILEX Anti-C5 MAb BB5-1 -- Alexion AngioMab - Antisoma Anti-C5 MAb N19-8 - Alexion Angiopoietins - Regeneron/Procter & Anti-C8 MAb Gamble anticancer cytokines -- BioPulse angiostatin - EntreMed Angiostatin/endostatin gene therapy anticancer matrix - Telios Integra Anticancer monoclonal antibodies - ARIUS. Genetix Pharmaceuticals angiotensin-II, topical -- Maret **Immunex** anticancer peptides - Maxygen, Micrologix Anthrax - EluSvs Therapeutics/US Army Anticancer prodrug Tech. -- Alexion Medical Research Institute Antibody Technologies Anthrax vaccine Anti platelet-derived growth factor D human anticancer Troy-Bodies -- Affite -- Affitech anticancer vaccine - NIH monoclonal antibodies -- CuraGen Anti-17-1A MAb 3622W94 -anticancers - Epimmune Anti-CCR5/CXCR4 sheep MAb - KS GlaxoSmithKline Biomedix Holdinas Anti-2C4 MAb -- Genentech anti-4-1BB monoclonal antibodies -- Bristol- Anti-CD11a MAb KBA --Anti-CD11a MAb M17 Mvers Squibb Anti-CD11a MAb TA-3 -Anti-Adhesion Platform Tech. - Cytovax Anti-adipocyte MAb - Cambridge Antibody Anti-CD11a MAb WT.1 -Anti-CD11b MAb -- Pharmacia Tech./ObeSvs Anti-CD11b MAb LM2 antiallergics -- Maxygen antiallerov vaccine - Acambis Anti-CD154 MAb -- Biogen Anti-alpha-4-integrin MAb Anti-CD16-anti-CD30 MAb -- Biotest Anti-CD18 MAb - Pharmacia Anti-alphavB3 integrin MAb - Applied Anti-CD19 MAb B43 -Molecular Evolution

FIG. 28B

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Anti-CD19 MAb -liposomal sodium butyrate Anti-CD4 MAb 4162W94 -- GlaxoSmithKline conjugate -Anti-CD4 MAb B-F5 - Diaclone Anti-CD147 Anti-CD4 MAb GK1-5 Anti-CD19 MAb-saporin conjugate -Anti-CD4 MAh KT6 Anti-CD19-dsEv-PE38-immunotoxin -Anti-CD4 MAb OX38 Anti-CD2 MAh 12-15 -Anti-CD4 MAb PAP conjugate - Bristol-Anti-CD2 MAb B-E2 -- Diaclone Myers Squibb Anti-CD2 MAb OX34 -Anti-CD4 MAb RIB 5-2 Anti-CD2 MAb OX54 -Anti-CD4 MAb W3/25 Anti-CD2 MAb OX55 -Anti-CD4 MAb YTA 3.1.2 Anti-CD2 MAb RM2-1 Anti-CD4 MAb YTS 177-9 Anti-CD2 MAb RM2-2 Anti-CD40 ligand MAb 5c8 -- Biogen Anti-CD2 MAb RM2-4 Anti-CD40 MAb Anti-CD20 MAb BCA B20 Anti-CD40 MAb 5D12 - Tanox Anti-CD20-anti-Fc alpha RI bispecific MAb -Anti-CD44 MAb A3D8 Medarex, Tenovus Anti-CD44 MAh GKWA3 Anti-CD22 MAb-saporin-6 complex -Anti-CD44 MAb IM7 Antl-CD3 immunotoxin -Anti-CD44 MAb KM81 Anti-CD3 MAb 145-2C11 - Pharming Anti-CD44 variant monoclonal antibodies --Anti-CD3 MAb CD4lgG conjugate --Corixa/Hebrew University Genentech Anti-CD45 MAb BC8-I-131 Anti-CD3 MAb humanised - Protein Design, Anti-CD45RB MAb RW Johnson Anti-CD48 MAb HuLv-m3 Anti-CD3 MAb WT32 Anti-CD48 MAb WM-63 Anti-CD5 MAb -- Becton Dickinson Anti-CD3 MAb-ricin-chain-A conjugate -Anti-CD3 MAb-xanthine-oxidase conjugate Anti-CD5 MAb OX19 Anti-CD6 MAb Anti-CD30 MAb BerH2 -- Medac Anti-CD7 MAb-PAP conjugate Anti-CD7 MAb-ricin-chain-A conjugate Anti-CD30 MAb-saporin conjugate Anti-CD30-scFv-ETA'-immunotoxin Anti-CD8 MAb - Amerimmune, Cytodyn, Anti-CD38 MAb AT13/5 Becton Dickinson Anti-CD38 MAb-saporin conjugate Anti-CD8 MAb 2-43 Anti-CD3-anti-CD19 bispecific MAb Anti-CD8 MAb OX8 Anti-CD3-anti-EGFR MAb Anti-CD80 MAb P16C10 -- IDEC Anti-CD3-anti-interleukin-2-receptor MAb Anti-CD80 MAb P7C10 - ID Vaccine Anti-CD3-anti-MOv18 MAb -- Centocor Anti-CD8-idarubicin conjugate Anti-CD3-anti-SCLC bispecific MAb Anti-CEA MAb CE-25 Anti-CD4 idiotype vaccine Anti-CEA MAb MN 14 – Immunomedics Anti-CD4 MAb - Centocor, IDEC Anti-CEA MAb MN14-PE40 conjugate -Pharmaceuticals, Xenova Group Immunomedics

Anti-CD4 MAb 16H5

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Anti-heparanase human monoclonal Anti-CEA MAb T84.66-interleukin-2 conjugate antibodies - Oxford Glycosciences/Medarex Anti-CEA sheep MAb -- KS Biomedix Anti-hepatitis C virus human monoclonal Holdings antihodies -- XTL Biopharmaceuticals Anti-cell surface monoclonal antibodies -Cambridge Antibody Tech. /Pharmacia Anti-HER-2 antibody gene therapy Anti-c-erbB2-anti-CD3 bifunctional MAb --Anti-herpes antibody – Epicyte Anti-HIV antibody -- Epicyte Otsuka anti-HIV catalytic antibody -- Hesed Biomed Anti-CMV MAb -- Scotgen anti-HIV fusion protein -- Idun Anti-complement anti-HIV proteins - Cangene Anti-CTLA-4 MAb Anti-HM1-24 MAb -- Chugai Anti-EGFR catalytic antibody -- Hesed Anti-hR3 MAb Anti-Human-Carcinoma-Antigen MAb -anti-EGFR immunotoxin -- IVAX Epicyte Anti-EGFR MAb -- Abgenix Anti-ICAM-1 MAb -- Boehringer Ingelheim Anti-EGFR MAb 528 Anti-EGFR MAb KSB 107 -- KS Biomedix . Anti-ICAM-1 MAb 1A-29 -- Pharmacia Anti-EGFR MAb-DM1 conjugate --Anti-ICAM-1 MAb HA58 Anti-ICAM-1 MAb YN1/1.7.4 ImmunoGen Anti-ICAM-3 MAb ICM3 -- ICOS Anti-EGFR MAb-LA1 --Anti-EGFR sheep MAb -- KS Biomedix Anti-idiotype breast cancer vaccine 11D10 Anti-idiotype breast cancer vaccine Anti-FAP MAb F19-I-131 ACA14C5 --Anti-Fas IgM MAb CH11 Anti-idiotype cancer vaccine -- ImClone Anti-Fas MAb Jo2 Systems/Merck KGaA ImClone, Viventia Anti-Fas MAb RK-8 Anti-Fit-1 monoclonal antibodies -- ImClone Biotech Anti-idiotype cancer vaccine 1A7 -- Titan Anti-fungal peptides -- State University of Anti-idiotype cancer vaccine 3H1 -- Titan New York Anti-idiotype cancer vaccine TriAb -- Titan antifungal tripeptides - BTG Anti-ganglioside GD2 antibody-interleukin-2 Anti-idiotype Chlamydia trachomatis vaccine fusion protein - Lexigen Anti-idiotype colorectal cancer vaccine --Anti-GM2 MAb -- Kyowa Anti-GM-CSF receptor monoclonal Novartis antibodies -- AMRAD Anti-idiotype colorectal cancer vaccine -Anti-gp130 MAb -- Tosoh Onvvax Anti-idiotype melanoma vaccine - IDEC Anti-HCA monoclonal antibodies --**Pharmaceuticals** AltaRex/Epigen Anti-hCG antibodies - Abgenix/AVI Anti-idiotype ovarian cancer vaccine ACA RioPharma Anti-idiotype ovarian cancer vaccine AR54 -AltaRex

FIG. 28D

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Anti-L-selectin monoclonal antibodies -Anti-idiotype ovarian cancer vaccine CA-125 – AltaRex, Biomira Protein Design Labs, Abgenix, Stanford Anti-loE catalytic antibody - Hesed Biomed University Anti-IgE MAb E26 - Genentech Anti-MBL monoclonal antibodies --Anti-IGF-1 MAb Alexion/Brigham and Women's Hospital anti-inflammatory -- GeneMax Anti-MHC monoclonal antibodies anti-inflammatory peptide - BTG Anti-MIF antibody humanised - IDEC, Cytokine PharmaSciences anti-integrin peptides - Burnha Anti-interferon-alpha-receptor MAb 64G12 - Anti-MRSA/VRSA sheep MAb - KS Biomedix Holdinas Pharma Pacific Management Anti-interferon-gamma MAb - Protein Anti-mu MAb -- Novartis Anti-MUC-1 MAb Design Labs Anti-interferon-gamma polyclonal antibody - Anti-MUC 18 Anti-Nogo-A MAb IN1 Advanced Biotherapy Anti-nuclear autoantibodies -- Procyon Anti-interleukin-10 MAb --Anti-ovarian cancer monoclonal antibodies -Anti-interleukin-12 MAb --Anti-interleukin-1-beta polyclonal antibody -- - Dompe Anti-p185 monoclonal antibodies R&D Systems Anti-interleukin-2 receptor MAb 2A3 Anti-p43 MAb Anti-interleukin-2 receptor MAb 33B3-1 -Antiparasitic vaccines Anti-PDGF/bFGF sheep MAb -- KS Immunotech Anti-interleukin-2 receptor MAb ART-18 Biomedix Anti-interleukin-2 receptor MAb LO-Tact-1 Anti-properdin monoclonal antibodies --Abgenix/Gliatech Anti-interleukin-2 receptor MAb Mikbeta1 Anti-interleukin-2 receptor MAb NDS61 Anti-PSMA (prostrate specific membrane Anti-interleukin-4 MAb 11B11 antigen) Anti-PSMA MAb J591 -- BZL Biologics Anti-interleukin-5 MAb - Wallace Anti-Rev MAb gene therapy -Laboratories Anti-interleukin-6 MAb - Centocor, Anti-RSV antibodies - Epicyte, Intracell Anti-RSV monoclonal antibodies --Diaclone, Pharmadiam Medarex/Medimmune, Applied Molecular Anti-interleukin-8 MAb - Abgenix Anti-interleukin-8 MAb - Xenotech Evolution/MedImmune Anti-RSV MAb. inhalation -Anti-JL1 MAb Alkermes/Medimmune Anti-Klebsiella sheep MAb -- KS Biomedix Anti-RT gene therapy Anti-Laminin receptor MAb-liposomal Antisense K-ras RNA gene therapy doxorubicin conjugate Anti-SF-25 MAb Anti-LCG MAb -- Cytoclonal Anti-sperm antibody -- Epicyte Anti-lipopolysaccharide MAb - VitaResc Anti-Tac(Fv)-PE38 conjugate

FIG. 28E

Anti-TAPA/CD81 MAb AMP1 Anti-tat gene therapy

AOP-RANTES - Senetek Anti-TCR-alphabeta MAb H57-597 Apan-CH - Praecis Pharmaceuticals Anti-TCR-alphabeta MAb R73 APC-8024 -- Demegen Anti-tenascin MAb BC-4-I-131 Anti-TGF-beta human monoclonal ApoA-1 - Milano, Pharmacia antibodies -- Cambridge Antibody Tech., Apogen -- Alexion apolipoprotein A1 -- Avanir Genzyme Apolipoprotein E - Bio-Tech. General Anti-TGF-beta MAb 2G7 - Genentech Antithrombin III - Genzyme Transgenics, Applaggin - Biogen aprotinin - ProdiGene Aventis, Bayer, Behringwerke, CSL, APT-070C -- AdProTech Myriad AR 177 - Aronex Pharmaceuticals Anti-Thy1 MAb AR 209 -- Áronex Pharmaceuticals. Anti-Thy1.1 MAb Antigenics Anti-tissue factor/factor VIIA sheep MAb -AR545C KS Biomedix ARGENT gene delivery systems - ARIAD Anti-TNF monoclonal antibodies -Arresten Centocor, Chiron, Peptech, Pharacia, ART-123 - Asahi Kasei Serono arvisulfatase B -- BioMarin Anti-TNF sheep MAb -- KS Biomedix Arylsulfatase B, Recombinant human --Holdings Anti-TNFalpha MAb -- Genzyme BioMarin Anti-TNFalpha MAb B-C7 - Diacione AS 1051 - Aijnomoto Anti-tooth decay MAb - Planet BioTech. ASI-BCL -- Intracell Asparaginase - Merck Anti-TRAIL receptor-1 MAb -- Takeda ATL-101 - Alizyme Antitumour RNases - NIH Atrial natriuretic peptide - Pharis Anti-VCAM MAb 2A2 - Alexion Aurintricarboxylic acid-high molecular Anti-VCAM MAb 3F4 - Alexion weight Anti-VCAM-1 MAb Autoimmune disorders -- GPC Anti-VFC MAb - ImClone Biotech/MorphoSys Anti-VEGF MAb -- Genentech Autoimmune disorders and transplant Anti-VEGF MAb 2C3 rejection -- Bristol-Myers Squibb/Genzyme Anti-VEGF sheep MAb - KS Biomedix Holdings Autoimmune disorders/cancer --Anti-VLA-4 MAb HP1/2 -- Biogen Abgenix/Chiron, CuraGen Anti-VI A-4 MAb PS/2 Autotaxin Anti-VLA-4 MAb R1-2 Avicidin -- NeoRx Anti-VLA-4 MAb TA-2 axogenesis factor-1 - Boston Life Sciences Anti-VAP-1 human MAb Anti-VRE sheep MAb -- KS Biomedix Axokine - Regeneron B cell lymphoma vaccine - Biomira Holdings B7-1 gene therapy -ANUP -- TranXenoGen ANUP-1 -- Pharis BABS proteins - Chiron

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BMP 2 - Genetics Institute/Medtronic-BAM-002 - Novelos Therapeutics Basiliximab (anti CD25 MAb) - Novartis Sofamor Danek, Genetics Institute/ Collagenesis, Genetics Bay-16-9996 -- Bayer Institute/Yamanouch Bay-39-9437 - Bayer BMP 2 gene therapy Bay-50-4798 - Bayer BMP 52 -- Aventis Pasteur, Biopharm BB-10153 - British Biotech BMP-2 - Genetics Institute BRT-001 - Bolder BioTech. BMS 182248 - Bristol-Myers Squibb BBT-002 -- Bolder BioTech. BMS 202448 -- Bristol-Myers Squibb BBT-003 - Bolder BioTech. bone growth factors - IsoTis BBT-004 - Bolder BioTech. BBT-005 - Bolder BioTech. BPC-15 -- Pfizer BBT-006 -- Bolder BioTech. brain natriuretic peptide -Breast cancer - Oxford BBT-007 - Bolder BioTech. GlycoSciences/Medarex BCH-2763 -- Shire Breast cancer vaccine - Therion Biologics, BCSF - Millenium Biologix BDNF - Regeneron - Amgen Oregon Becaplermin -- Johnson & Johnson, Chiron BSSL -- PPL Therapeutics BST-2001 - BioStratum Bectumomab - immunomedics BST-3002 -- BioStratum Beriplast -- Aventis BTI 322 -Beta-adrenergic receptor gene therapy butyryicholinesterase - Shire University of Arkansas C 6822 -- COR Therapeutics bFGF - Scios C1 esterase inhibitor -- Pharming BI 51013 -- Behringwerke AG BIBH 1 - Boehringer Ingelheim C3d adjuvant - AdProTech BIM-23190 - Beaufour-Ipsen CAB-2.1 - Millennium birch pollen immunotherapy -- Pharmacia calcitonin - Inhale Therapeutics Systems, Aventis, Genetronics, TranXenoGen, bispecific fusion proteins - NtH Unigene, Rhone Poulenc Rohrer Bispecific MAb 2B1 -- Chiron calcitonin - oral - Nobex, Emisphere. Pharmaceutical Discovery BIWA 4 -- Boehringer Ingelheim Calcitonin gene-related peptide - Asahi blood substitute -- Northfield, Baxter Intl. Kasei - Unigene BLP-25 -- Biomira calcitonin, human -- Suntory BI S-0597 - Boston Life Sciences calcitonin, nasal - Novartis, Unigene BLyS -- Human Genome Sciences calcitonin, Panoderm - Elan BLvS radiolabelled - Human Genome calcitonin, Peptitrol - Shire Sciences calcitonin, salmon - Therapicon BM 06021 – Boehringer Mannheim calin - Biopharm BM-202 -- BioMarin Calphobindin I BM-301 -- BioMarin calphobindin I -- Kowa BM-301 -- BioMarin calreticulin -- NYU BM-302 -- BioMarin

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CD4 fusion toxin - Senetek Campath-1G CD4 laG -- Genentech Campath-1M cancer therapy -- Cangene cancer vaccine - Aixlie, Aventis Pasteur, Center of Molecular Immunology, YM BioSciences, Cytos, Genzyme, CD40 ligand - Immunex Transgenics, Globelmmune, Igeneon; ImClone, Virogenetics, InterCell, Iomai, Jenner Biotherapies, Memorial Sloan-Kettering Cancer Center, Sydney Kimmel Cancer Center, Novavax, Protein CD8. soluble -- Avidex CD95 ligand -- Roche Sciences, Argonex, SIGA CDP 571 - Celitech Cancer vaccine AI VAC-CEA B7.1 --CDP 850 - Celltech Aventis Pasteur/Therion Biologics Cancer vaccine CEA-TRICOM -- Aventis CDP 870 -- Celltech Pasteur/Therion Biologics Cancer vaccine gene therapy - Cantab Pharmaceuticals Cancer vaccine HER-2/neu -- Corixa Cetermin -- Insmed CETP vaccine -- Avant Cancer vaccine THERATOPE - Biomira Cetrorelix cancer vaccine. PolyMASC -- Valentis Cetuximab Candida vaccine - Corixa, Inhibitex CGH 400 -- Novartis Canstatin - ILEX CAP-18 -- Panorama CGP 42934 - Novartis Cardiovascular gene therapy - Collateral CGP 51901 - Tanox CGRP - Unigene Therapeutics CGS 27913 -- Novartis carperitide - Suntory CGS 32359 - Novartis Casocidin-1 -- Pharis CAT 152 - Cambridge Antibody Tech. CAT 192 - Cambridge Antibody Tech. CHH 380 -- Novartis CAT 213 - Cambridge Antibody Tech. Catalase -- Enzon Cat-PAD - Circassia Biologics CB 0006 - Celltech CCK(27-32)--- Akzo Nobel **Biologics** CCR2-641 -- NIH CD, Procept -- Paligent CD154 gene therapy Serum and Vaccine Institute Berne CD39 -- Immunex Cholera vaccine CVD 112 -- Swiss Serum CD39-L2 - Hysea CD39-L4 -- Hysea and Vaccine Institute Berne

CD4 receptor antagonists -Pharmacopeia/Progenics CD4 soluble -- Progenics CD4. soluble - Genzyme Transgenics CD4-ricin chain A - Genentech CD59 gene therapy -- Alexion CD8 TIL cell therapy - Aventis Pasteur CDP-860 (PEG-PDGF MAb) -- Celltech CDS-1 -- Emest Orlando Cedelizumab -- Ortho-McNeil Chagas disease vaccine -- Corixa chemokines -- Immune Response chitinase - Genzyme, ICOS Chlamydia pneumoniae vaccine -- Antex Chlamydia trachomatis vaccine -- Antex Chlamydia vaccine - GlaxoSmithKline Cholera vaccine CVD 103-HgR -- Swiss

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Cholera vaccine inactivated oral - SBL CRL 1605 - CytRx CS-560 - Sankyo CSF -- ZymoGenetics Chrysalin - Chrysalis BioTech. CI-782 - Hitachi Kase CSF-G - Hangzhou, Dong-A, Hanmi Ciliary neurotrophic factor - Fidia, Roche CSF-GM - Cangene, Hunan, LG Chem. CSF-M -- Zarix CIM project - Active Biotech CL 329753 - Wyeth-Ayerst CT 1579 - Merck Frosst CT 1786 - Merck Frosst CL22. Cobra - ML Laboratories CT-112* - BTG Clenoliximab - IDEC Clostridium difficile antibodies - Epicyte CTB-134L - Xenova CTC-111 - Kaketsuken clotting factors -- Octagene CTGF - FibroGen CMB 401 - Celitech CTLA4-Ig - Bristol-Myers Squibb CNTF -- Sigma-Tau CTLA4-lg gene therapy --Cocaine abuse vaccine - Cantab, CTP-37 - AVI BioPharma ImmuLogic, Scripps C-type natriuretic peptide - Suntory coccidiomycosis vaccine - Arizo CVS 995 - Corvas Intl. collagen - Type I - Pharming CX 397 - Nikko Kvodo Collagen formation inhibitors - FibroGen Collagen/hydroxyapatite/bone growth factor CY 1747 - Epimmune - Aventis Pasteur, Biopharm, Orquest CY 1748 -- Epimmune collagenase -- BioSpecifics Cvanovirin-N Colorectal cancer vaccine -- Wistar Institute Cystic fibrosis therapy -- CBR/IVAX Component B, Recombinant -- Serono CYT 351 Connective tissue growth factor inhibitors -- cytokine Traps -- Regeneron cytokines - Enzon, Cytoclonal FibroGen/Taisho Cytomegalovirus glycoprotein vaccine --Contortrostatin Chiron, Aquila Biopharmaceuticals, contraceptive vaccine -- Zonagen Aventis Pasteur, Virogenetics Contraceptive vaccine hCG Contraceptive vaccine male reversible -Cytomegalovirus vaccine live - Aventis Pasteur IMMUCON Contraceptive vaccine zona pellucida -Cytosine deaminase gene therapy -GlaxoSmithKline DA-3003 -- Dong-A Copper-64 labelled MAb TETA-1A3 -- NCI DAB389interleukin-6 - Senetek Coralyne DAB389interleukin-7 Corsevin M Daclizumab (anti-IL2R MAb) - Protein C-peptide analogues -- Schwarz Design Labs CPI-1500 - Consensus CRF - Neurobiological Tech. DAMP^ -- Incyte Genomics cRGDfV pentapeptide --Daniplestim -- Pharmacia darbepoetin alfa - Amgen CRL 1095 - CvtRx CRL 1336 - CytRx DBI-3019 - Diabetogen

FIG. 281

Duteplase - Baxter Intl. DCC -- Genzyme DWP-401 - Daewoong DDF -- Hyseq decorin - Integra, Telios DWP-404 - Daewoong defensins -- Large Scale Biology DWP-408 -- Daewoong Dx 88 (Epi-KAL2) - Dyax DEGR-VIIa Dx 890 (elastin inhibitors) - Dyax Delmmunised antibody 3B6/22 AGEN Deimmunised anti-cancer antibodies -E coli O157 vaccine - NIH E21-R -- BresaGen Biovation/Viragen Eastern equine encephalitis virus vaccine -Dendroamide A Dengue vaccine -- Bavarian Nordic, Merck Echicetin --Echinhibin 1 -denileukin diftitox -- Ligand Fchistatin - Merck DES-1101 - Desmos Fchitamine desirudin -- Novartis Ecromeximab - Kyowa Hakko desmopressin -- Unigene FC-SOD -- PPL Therapeutics Desmoteplase - Merck, Schering AG Eculizumab (5G1.1) -- Alexion Destabilase Diabetes gene therapy - DeveloGen, Pfizer EDF - Allnomoto FDN derivative - NIH Diabetes therapy -- Crucell EDNA -- NIH Diabetes type 1 vaccine - Diamvd Edobacomab -- XOMA Therapeutics Edrecolomab -- Centocor DiaCIM -- YM BioSciences FF 5077 dialytic oligopeptides - Research Corp Efalizumab - Genentech Diamyd -- Diamyd Therapeutics EGF fusion toxin - Seragen, Ligand DiaPen227-- Pepgen EGF-P64k vaccine - Center of Molecular DiavaX - Corixa **Immunology** Digoxin MAb -- Glaxo Diphtheria tetanus pertussis-hepatitis B EL 246 - LigoCyte elastase inhibitor - Synergen vaccine - GlaxoSmithKline elcatonin - Therapicon DIR therapy - Solis Therapeutics -FMD 72000 - Merck KGaA DNase - Genentech Emdogain -- BIORA Dornase alfa -- Genentech emfilermin - AMRAD Dornase alfa, inhalation - Genentech Emoctakin - Novartis Doxorubicin-anti-CEA MAb conjugate enamel matrix protein - BIORA **Immunomedics** Endo III -- NYU DP-107 - Trimeris endostatin -- EntreMed, Pharis drotrecogin alfa - Eli Lilly Enhancins -- Micrologix DTctGMCSF Enlimomab - Isis Pharm. DTP-polio vaccine - Aventis Pasteur Enoxaparin sodium -- Pharmuka DU 257-KM231 antibody conjugate -enzyme linked antibody nutrient depletion Kvowa therapy -- KS Biomedix Holdings dural graft matrix - Integra

FIG. 28J

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Factor VII - Novo Nordisk, Bayer, Baxter Eosinophil-derived neutralizing agent ~ EP-51216 -- Asta Medica Factor VIIa - PPL Therapeutics, FP-51389 -- Asta Medica EPH family ligands - Regeneron ZvmoGenetics Epidermal growth factor - Hitachi Kasei. Factor VIII - Bayer Genentech, Beaufour-Ipsen, CLB, Inex, Octagen, Pharmacia, Johnson & Johnson Epidermal growth factor fusion toxin-Pharming Senetek Factor VIII -- PEGylated -- Bayer Factor VIII fragments - Pharmacia Epidermal growth factor-genistein -Factor VIII gene therapy - Targeted EPI-HNE-4 - Dvax Genetics EPI-KAL2 -- Dyax Factor VIII sucrose formulation - Bayer, Epoetin-alfa -- Amgen, Dragon Genentech Pharmaceuticals, Nanjing Huaxin Factor VIII-2 -- Baver Epratuzumab - Immunomedics Factor VIII-3 -- Bayer Epstein-Barr virus vaccine --Aviron/SmithKline Beecham, Bioresearch Factor Xa inhibitors - Merck, Novo Nordisk, Mochida Eptacog alfa - Novo Nordisk Factor XIII -- ZymoGenetics Eptifibatide - COR Therapeutics Factors VIII and IX gene therapy -- Genetics erb-38 --Erlizumab -- Genentech Institute/Targeted Genetics erythropoietin -- Alkermes, ProLease, Dong-Famoxin -- Genset Fas (delta) TM protein - LXR BioTech. A. Elanex, Genetics Institute, LG Chem, Fas TR -- Human Genome Sciences Protein Sciences, Serono, Snow Brand, Felvizumab -- Scotgen SRC VB VECTOR, Transkaryotic FFR-VIIa - Novo Nordisk Therapies FG-001 - F-Gene Erythropoietin Beta -- Hoffman La Roche FG-002 - F-Gene Erythropoietin/Epoetin alfa -- Chugai Escherichia coli vaccine -- North American FG-004 - F-Gene FG-005 - F-Gene Vaccine, SBL Vaccin, Swiss Serum and FGF + fibrin -- Repair Vaccine Institute Berne Fibrimage -- Bio-Tech, General etanercept - Immunex examorelin - Mediolanum fibrin-binding peptides - ISIS Innovation Exendin 4 -- Amylin fibringen - PPL Therapeutics, Pharming fibroblast growth factor - Chiron, NYU, exonuclease VII Ramot, ZymoGenetics F 105 -- Centocor fibrolase conjugate - Schering AG F-992 -- Fornix Filgrastim -- Amgen Factor IX - Alpha Therapeutics, Welfide filgrastim - PDA modified -- Xencor Corp., CSL, enetics institute/AHP. FLT-3 ligand - Immunex Pharmacia, PPL Therapeutics FN18 CRM9 -Factor IX gene therapy - Cell Genesys

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glutamate decarboxylase -- Genzyme follistatin - Biotech Australia, Human Transgenics Therapeutics Glycoprotein S3 - Kureha follitropin alfa – Alkermes, ProLease, GM-CSF - Immunex PowderJect, Serono, Akzo Nobel GM-CSF tumour vaccine -- PowderJect Follitropin Beta - Bayer, Organon GnRH immunotherapeutic -- Protherics FP 59 Goserelin (LhRH antagonist) - AstraZeneca FSH -- Ferring ap75 antigen - ImClone FSH + LH -- Ferring ap96 -- Antigenics F-spondin -- CeNeS fusion protein delivery system - UAB GPI 0100 -- Galenica GR 4991W93 -- GlaxoSmithKline Research Foundation Granulocyte colony-stimulating factor -fusion toxins - Boston Life Sciences Dona-A G 5598 -- Genentech Granulocyte colony-stimulating factor GA-II -- Transkaryotic Therapies Gamma-interferon analogues -- SRC VB conjugate grass allergy therapy -- Dynavax VECTOR GRF1-44 -- ICN Ganirelix -- Roche Growth Factor - Chiron, Atrigel, Atrix, gastric lipase -- Meristem Innogenetics, ZymoGenetics, Novo Gavilimomab growth factor peptides -- Biotherapeutics G-CSF - Amgen, SRC VB VECTOR growth hormone -- LG Chem GDF-1 -- CeNeS growth hormone, Recombinant human -GDF-5 -- Biopharm Serono GDNF (glial derived neurotrophic factor) --GT 4086 -- Gliatech Amaen GW 353430 -- GlaxoSmithKline gelsolin - Biogen GW-278884 - GlaxoSmithKline Gemtuzumab ozogamicin -- Celltech Gene-activated epoetin-alfa -- Aventis H 11 -- Viventia Biotech H5N1 influenza A virus vaccine -- Protein Pharma - Transkarvotic Therapies Gianzmann thrombasthenia gene therapy -Sciences haemoglobin -- Biopure Glatiramer acetate - Yeda haemoglobin 3011, Recombinant -- Baxter glial growth factor 2 -- CeNeS Healthcare GLP-1 - Amylin, Suntory, TheraTech, haemoglobin crosfumarii - Baxter Intl. Watson haemoglobin stabilized - Alinomoto GLP-1 peptide analogues -- Zealand haemoglobin, recombinant -- Apex **Pharaceuticals** HAF - Immune Response alucación -- Eli Lilly, ZymoGenetics Hantavirus vaccine Glucagon-like peptide-1 7-36 amide --HB 19 Suntory HBNF -- Regeneron Glucogen-like peptide -- Amylin Glucocerebrosidase -- Genzyme HCC-1 -- Pharis hCG -- Milkhaus

FIG. 28L

hCG vaccine -- Zonagen HE-317 - Hollis-Eden Pharmaceuticals Heat shock protein cancer and influenza vaccines -- StressGen Helicobacter pylori vaccine - Acambis, AstraZeneca/CSL, Chiron, Provalis Helistat-G -- GalaGen Hemolink - Hemosol hepapoietin -- Snow Brand heparanase - InSight henarinase I -- Ibex heparinase III - lbex Hepatitis A vaccine -- American Biogenetic HIC 1 Sciences Hepatitis A vaccine inactivated Hepatitis A vaccine Nothay -- Chiron Hepatitis A-hepatitis B vaccine --GlaxoSmithKline hepatitis B therapy -- Tripep Hepatitis B vaccine -- Amgen, Chiron SpA, Meiji Milk, NIS, Prodeva, PowderJect, Rhein Biotech Hepatitis B vaccine recombinant - Evans Vaccines, Epitec Combiotech, Genentech, HIV gp160 DNA vaccine - PowderJect, Medimmune, Merck Sharp & Dohme, Rhein Biotech, Shantha Biotechnics, Vector, Yeda Hepatitis B vaccine recombinant TGP 943 -- HIV HGP-30W vaccine -- CEL-SCI Takeda Hepatitis C vaccine - Bavarian Nordic, Chiron, Innogenetics Acambis, Hepatitis D vaccine -- Chiron Vaccines Hepatitis E vaccine recombinant -Genelabs/GlaxoSmithKline, Novavax hepatocyte growth factor - Panorama. Sosei hepatocyte growth factor kringle fragments -- EntreMed Her-2/Neu peptides - Corixa

Herpes simplex glycoprotein DNA vaccine -Merck, Wyeth-Lederle Vaccines-Malvern, Genentech, GlaxoSmithKline, Chiron. Takeda Herpes simplex vaccine - Cantab Pharmaceuticals, CEL-SCI, Henderson Morley Herpes simplex vaccine live -- ImClone Systems/Wyeth-Lederle, Aventis Pasteur HGF derivatives -- Dompe hIAPP vaccine -- Crucell Hib-hepatitis B vaccine - Aventis Pasteur HIP-- Altachem Hirudins - Biopharma, Cangene, Dongkook, Japan Energy Corporation, Pharmacia Corporation, SIR International, Sanofi-Synthelabo, Sotragene, Rhein Biotech HIV edible vaccine -- ProdiGene HIV gp120 vaccine - Chiron, Ajinomoto, GlaxoSmithKline, ID Vaccine, Progenics, VaxGen HIV gp120 vaccine gene therapy -Aventis Pasteur, Oncogen, Hyland Immuno, Protein Sciences HIV gp41 vaccine -- Panacos HIV immune globulin - Abbott, Chiron HIV peptides - American Home Products HIV vaccine - Applied bioTech., Axis Genetics, Biogen, Bristol-Myers Squibb, Genentech, Korea Green Cross, NIS, Oncogen, Protein Sciences Corporation. Terumo, Tonen Corporation, Wyeth-Ayerst, Wyeth-Lederle Vaccines-Malvern, Advanced BioScience Laboratories. Bayarian Nordic, Bayarian Nordic/Statens Serum Institute, GeneCure, Immune Response, Progenics, Therion Biologics, United Biomedical, Chiron

FIG. 28M

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HIV vaccine vCP1433 -- Aventis Pasteur Human monoclonal antibodies -HIV vaccine vCP1452 -- Aventis Pasteur Medarex/Northwest Biotherapeutics, Medarex/Seattle Genetics HIV vaccine vCP205 -- Aventis Pasteur human netrin-1 -- Exelixis HL-9 -- American BioScience human papillomavirus antibodies -- Epicyte HM-9239 -- Cytran Human papillomavirus vaccine - Biotech HML-103 -- Hemosol Australia, IDEC, StressGen HMI -104 -- Hemosol Human papillomavirus vaccine MEDI 501 --HML-105 -- Hemosol Medimmune/GlaxoSmithKline HML-109 -- Hemosol Human papillomavirus vaccine MEDI HML-110 -- Hemosol 503/MEDI 504 --HML-121 -- Hemosol MedImmune/GlaxoSmithKline hNLP -- Pharis Human papillomavirus vaccine TA-CIN --Hookworm vaccine Cantab Pharmaceuticals host-vector vaccines - Henogen Human papillomavirus vaccine TA-HPV --HPM 1 -- Chugai HPV vaccine -- MediGene Cantab Pharmaceuticals Human papillomavirus vaccine TH-GW --HSA - Meristem Cantab/GlaxoSmithKline HSF -- StressGen human polyclonal antibodies -- Biosite/Eos HSP carriers -- Weizmann, Yeda, Peptor BioTech./ Medarex HSPPC-70 -- Antigenics HSPPC-96, pathogen-derived -- Antigenics human type II anti factor VIII monoclonal antibodies -- ThromboGenics HSV 863 -- Novartis humanised anti glycoprotein lb murine HTLV-I DNA vaccine monoclonal antibodies -- ThromboGenics HTLV-I vaccine HumaRAD -- Intracell HTLV-II vaccine -- Access HuMax EGFR -- Genmab HU 901 - Tanox HuMax-CD4 -- Medarex Hu23F2G -- ICOS HriMax-IL15 -- Genmab HuHMFG1 HYB 190 -- Hybridon HumaLYM - Intracell HYB 676 - Hybridon Human krebs statika - Yamanouchi I-125 MAb A33 -- Celltech human monoclonal antibodies -Ibritumomab tiuxetan -- IDEC Abgenix/Biogen, Abgenix/ Corixa, Abgenix/Immunex, Abgenix/Lexicon, IBT-9401 -- Ibex IBT-9402 -- Ibex Abgenix/ Pfizer, Athersys/Medarex, IC 14 - ICOS Biogen/MorphoSvs. CAT/Searle, Centocor/Medarex, Corixa/Kirin Brewery, Idarubicin anti-Ly-2.1 --IDEC 114 -- IDEC Corixa/Medarex, Eos BioTech./Medarex. IDEC 131 - IDEC Eos/Xenerex, Exelixis/Protein Design Labs, ImmunoGen/ Raven, Medarex/ IDEC 152 -- IDEC B.Twelve, MorphoSys/ImmunoGen, XTL IDM 1 -- IDM IDPS -- Hollis-Eden Pharmaceuticals Biopharmaceuticals/Dyax,

FIG. 28N

iduronate-2-sulfatase - Transkarvotic insulin -- AutoImmune, Altea, Biobras, BioSante, Bio-Tech, General, Chong Kun Therapies Dang, Emisphere, Flamel, Provalis, Rhein IGF/IBP-2-13 -- Pharis IGN-101 -- Igeneon Biotech, TranXenoGen insulin (bovine) - Novartis IK HIR02 -- Iketon insulin analogue -- Eli Lilly IL-11 - Genetics Institute/AHP Insulin Aspart - Novo Nordisk II -13-PE38 -- NeoPharm insulin detemir - Novo Nordisk IL-17 receptor -- Immunex IL-18BP - Yeda insulin glargine -- Aventis insulin inhaled - Inhale Therapeutics IL-1Hv1 -- Hvseq Systems, Alkermes IL-1ß -- Celltech IL-1ß adjuvant -- Celltech insulin oral -- Inovax IL-2 - Chiron insulin, AeroDose - AeroGen · IL-2 + IL-12 -- Hoffman La-Roche insulin, AERx -- Aradigm IL-6/sIL-6R fusion - Hadasit insulin, BEODAS - Elan IL-6R derivative -- Tosoh insulin, Biphasix -- Helix insulin, buccal - Generex IL-7-Dap 389 fusion toxin -- Ligand IM-862 - Cytran insulin, I2R - Flemington IMC-1C11 - ImClone insulin, intranasal -- Bentley insulin, oral - Nobex, Unigene imiglucerase -- Genzyme Immune globulin intravenous (human) -insulin, Orasome - Endorex insulin, ProMaxx -- Epic Hoffman La Roche immune privilege factor - Proneuron insulin, Quadrant - Elan Immunocal -- Immunotec insulin, recombinant - Aventis Immunogene therapy - Briana Bio-Tech insulin, Spiros -- Elan Immunoliposomal 5-fluorodeoxyuridinėinsulin, Transfersome - IDEA insulin, Zymo, recombinant -- Novo Nordisk dipalmitate -immun osuppressant vaccine - Aixlie insulinotropin -- Scios immunotoxin - Antisoma, NIH Insulysin gene therapy integrin antagonists -- Merck ImmuRAIT-Re-188 – Immunomedics imrea-1 -- Imrea interferon (Alpha2) -- SRC VB VECTOR, infertility -- Johnson & Johnson, E-TRANS Viragen, Dong-A, Hoffman La-Roche, Infliximab -- Centocor Genentech Influenza virus vaccine -- Aventis Pasteur, interferon - BioMedicines, Human Genome Protein Sciences Sciences inhibin -- Biotech Australia, Human interferon (Alfa-n3)-Interferon Sciences Therapeutics Inhibitory G protein gene therapy interferon (Alpha), Biphasix - Helix INKP-2001 -- InKine

Inolimomab -- Diaclone

IL-2/ diphtheria toxin - Ligand interferon (Alpha)-Amgen, BioNative, Interleukin-3 -- Cangene Novartis, Genzyme Transgenics, Hayashibara, Inhale Therapeutics Interleukin-4 - Immunology Ventures, Systems, Medusa, Flamel, Dong-A, Sanofi Winthrop, Schering-Plough, Immunex/ Sanofi Winthrop, Bayer, Ono GeneTrol. Nastech, Shantha, Wassermann, LG Chem, Sumitomo, interleukin-4 + TNF-Alpha -- NIH Aventis, Behring EGIS, Pepgen, Servier, interleukin-4 agonist -- Bayer interleukin-4 fusion toxin - Ligand Rhein Biotech. Interleukin-4 receptor - Immunex, Immun interferon (Alpha2A) interferon (Alpha2B) - Enzon, Schering-Interleukin-6 - Ajinomoto, Cangene, Yeda, Genetics Institute, Novartis Plough, Biogen, IDEA interferon (Alpha-N1) - GiaxoSmithKline interleukin-6 fusion protein interferon (beta) - Rentschler, GeneTrol, Interleukin-6 fusion toxin - Ligand, Serono Meristem, Rhein Biotech, Toray, Yeda, interleukin-7 -- IC Innovations interleukin-7 receptor -- Immunex Daiichi, Mochida interferon (Beta1A) - Serono, Biogen interleukin-8 antagonists -- Kyowa interferon (beta1A) inhale -- Biogen Hakko/Millennium/Pfizer interleukin-9 antagonists -- Genaera interferon (B1b)-- Chiron interleukin-10 - DNAX, Schering-Plough interferon (tau) - Pepgen Interleukin-10 gene therapy interferon alfacon-1 - Amgen interleukin-12 -- Genetics Institute, Hoffman Interferon alpha-2a vaccine La-Roche Interferon Beta 1b -- Schering/Chiron, interleukin-13 -- Sanofi InterMune interleukin-13 antagonists - AMRAD Interferon Gamma -- Boehringer ingelheim, Interleukin-13-PE38QQR Sheffield, Rentschler, Hayashibara interleukin-15 -- Immunex interferon receptor, Type I - Serono interleukin-16 - Research Corp interferon(Gamma1B) -- Genentech interleukin-18 - GlaxoSmithKline Interferon-alpha-2b + ribavirin - Biogen, Interleukin-18 binding protein -- Serono ICN lor-P3 -- Center of Molecular Immunology interferon-alpha-2b gene therapy --IP-10 - NIH Schering-Plough IPF -- Metabolex Interferon-con1 gene therapy --IR-501 -- Immune Response interleukin-1 antagonists -- Dompe ISIS 9125 - Isis Pharmaceuticais Interleukin-1 receptor antagonist - Abbott ISURF No. 1554 - Millennium Bioresearch, Pharmacia ISURF No. 1866 - Iowa State Univer. Interleukin-1 receptor type I - Immunex ITF-1697 -- Italfarmaco interleukin-1 receptor Type II -- Immunex IxC 162 - Ixion Interleukin-1 trap - Regeneron Interleukin-1-alpha - Immunex/Roche J 695 - Cambridge Antibody Tech., Genetics Inst., Knoli interleukin-2 - SRC VB VECTOR, Jagged + FGF - Repair Aiinomoto, Biomira, Chiron

FIG. 28P

JKC-362 -- Phoenix Pharmaceuticals leptin, 2nd-generation - Amgen JTP-2942 - Japan Tobacce leridistim - Pharmacia Juman monoclonal antibodies leuprolide, ProMaxx - Epic Medarex/Raven leuprorelin, oral - Unigene K02 - Axvs Pharmaceuticals LeuTech - Papatin LEX 032 - SuperGen Keliximab -- IDEC LiDEPT - Novartis Keyhole limpet haemocyanin Lintuzumab (anti-CD33 MAb) -- Protein KGF - Amgen KM 871 - Kyowa Design Labs KPI 135 -- Scios lipase - Altus Biologics lipid A vaccine -- EntreMed KPI-022 -- Scios lipid-linked anchor Tech. - ICRT, ID Kringle 5 Biomedical KSB 304 KSB-201 -- KS Biomedix liposome-CD4 Tech. - Sheffield L 696418 -- Merck Listeria monocytogenes vaccine L 703801 -- Merck LMB 1 L1 -- Acorda IMR 7 LMB 9 -- Battelle Memorial Institute, NIH L-761191 -- Merck lactoferrin - Meristem, Pharming, Agennix LM-CD45 -- Cantab Pharmaceuticals lovastatin -- Merck lactoferrin cardio - Pharming LSA-3 LAG-3 -- Serono LAIT - GEMMA LT-ß receptor -- Biogen lung cancer vaccine - Corixa LAK cell cytotoxin -- Arizona lamellarins - PharmaMar/University of lusupultide - Scios L-Vax -- AVAX Malaga laminin A peptides - NIH LY 355455 - Eli Lilly lanoteplase -- Genetics Institute LY 366405 -- Eli Lilly Iaronidase - BioMarin LY-355101 -- Eli Lilly Lyme disease DNA vaccine -- Vical/Aventis Lassa fever vaccine LCAT -- NIH Pasteur LDP 01 -- Millennium Lyme disease vaccine -- Aquila Biopharmaceuticals, Aventis, Pasteur, LDP 02 -- Millennium Symbicom, GlaxoSmithKline, Hyland Lecithinized superoxide dismutase -Immuno, Medimmune Seikagaku Lymphocytic chorlomeningitis virus vaccine LeIF adjuvant -- Corixa leishmaniasis vaccine -- Corixa lymphoma vaccine – Biomira, Genitope LYP18 lenercept - Hoffman La-Roche lys plasminogen, recombinant Lenograstim -- Aventis, Chugai lepirudin -- Aventis Lysosomal storage disease gene therapy -leptin - Amgen, IC Innovations Avigen

FIG. 28Q

M 23 -- Gruenenthal MEDI 507 - BioTransplant M1 monoclonal antibodies - Acorda melanin concentrating hormone --Neurocrine Biosciences Therapeutics MA 16N7C2 - Corvas Intl. melanocortins - OMRF malaria vaccine - GlaxoSmithKline. Melanoma monoclonal antibodies - Viragen melanoma vaccine - GlaxoSmithKline. AdProTech, Antigenics, Apovia, Aventis Pasteur, Axis Genetics, Behringwerke, Akzo Nobel, Avant, Aventis Pasteur, Bayarian Nordic, Biovector, CancerVax, CDCP, Chiron Vaccines, Genzyme Transgenics, Hawaii, Medimmune, NIH. Genzyme Molecular Oncology, Humbolt, NYU, Oxxon, Roche/Saramane, Biotech ImClone Systems, Memorial, NYU, Oxxon Melanoma vaccine Magevac -- Therion Australia, Rx Tech Malaria vaccine CDC/NIIMALVAC-1 memory enhancers - Scios meningococcal B vaccine -- Chiron malaria vaccine, multicomponent meningococcal vaccine - CAMR mammaglobin -- Corixa Meningococcal vaccine group B conjugate mammastatin -- Biotherapeutics - North American Vaccine mannan-binding lectin - Natlmmu mannan-MUC1 -- Psiron Meningococcal vaccine group B MAP 30 recombinant - BioChem Vaccines. Marinovir - Phytera Microscience Meningococcal vaccine group Y conjugate -MARstem -- Maret North American Vaccine MB-015 - Mochida Meningococcal vaccine groups A B and C MBP -- ImmuLogic conjugate - North American Vaccine MCI-028 -- Mitsubishi-Tokyo MCIF - Human Genome Sciences Mepolizumab - GlaxoSmithKline Metastatin - EntreMed. Takeda MDC - Advanced BioScience - Akzo Met-CkB7 -- Human Genome Sciences Nobel, ICOS MDX 11 -- Medarex met-enkephalin -- TNI METH-1 - Human Genome Sciences MDX 210 - Medarex methioninase - AntiCancer MDX 22 -- Medarex Methionine lyase gene therapy --MDX 22 MDX 240 -- Medarex AntiCancer Met-RANTES - Genexa Biomedical. MDX 33 MDX 44 -- Medarex Serono MDX 447 - Medarex Metreleptin Microtubule inhibitor MAb MDX H210 - Medarex Immunogen/Abgenix MDX RA -- Houston BioTech., Medarex MF-104 - Pharmexa MGDF -- Kirin MGV - Progenics Measles vaccine Mecasermin - Cephalon/Chiron, Chiron micrin -- Endocrine microplasmin - ThromboGenics MEDI 488 -- Medimmune MIF -- Genetics Institute MEDI 500

FIG. 28R

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MAb 45-2D9- - haematoporphyrin migration inhibitory factor -- NIH Mim CD4.1 - Xvcte Therapies conjugate mirostipen -- Human Genome Sciences MAb 4B4 Mitumomab (BEC-2) - ImClone Systems, MAb 4E3-CPA conjugate -- BCM Oncologia MAb 4E3-daunorubicin conjugate Merck KGaA MAb 50-6 MK 852 - Merck MLN 1202 (Anti-CCR2 monoclonal MAh 50-61A - Institut Pasteur antibody) - Millenium Pharmaceuticals MAb 5A8 - Biogen MAb 791T/36-methotrexate conjugate Mobenakin - NIS molgramostim -- Genetics Institute, Novartis MAb 7c11.e8 monoclonal antibodies -- Abgenix/Celltech, MAb 7E11 C5-selenocystamine conjugate MAb 93KA9 - Novartis Immusol/ Medarex, Viragen/ Roslin Institute, Cambridge Antibody Tech./Elan MAb A5B7-cisplatin conjugate --Biodynamics Research, Pharmacia MAb 108 -MAb A5B7-I-131 MAb 10D5 -MAb 14,18-interleukin-2 immunocytokine - MAb A7 MAb A717 -- Exocell Lexiaen MAb A7-zinostatin conjugate MAb 14G2a -MAb ABX-RB2 - Abgenix MAb 15A10 --MAb 170 -- Biomira MAb: ACA 11 MAb AFP-I-131 - Immunomedics MAb 177Lu CC49 --MAb AP1 MAb 17F9 MAb AZ1 MAb 1D7 MAb B3-LvsPE40 conjugate MAb 1F7 - Immune Network MAb B4 - United Biomedical MAb 1H10-doxorubicin conjugate MAb B43 Genistein-conjugate MAb 26-2F MAb B43.13-Tc-99m - Biomira MAb 2A11 MAb 2E1 - RW Johnson MAb B43-PAP conjugate MAb B4G7-gelonin conjugate MAb 2F5 MAb BCM 43-daunorubicin conjugate -MAb 31.1 - International BioImmune BCM Oncologia Systems MAb 32 - Cambridge Antibody Tech., MAb BIS-1 MAb BMS 181170 -- Bristol-Myers Squibb Peptech MAb 323A3 - Centocor MAb BR55-2 MAb BW494 MAb 3C5 MAb C 242-DM1 conjugate -- ImmunoGen MAb 3F12 MAb C242-PE conjugate MAb 3F8 MAb c30-6 MAb 42/6 MAb CA208-cytorhodin-S conjugate --MAb 425 - Merck KGaA Hoechst Japan MAb 447-52D - Merck Sharp & Dohme MAb CC49 -- Enzon

FIG. 28S

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MAb ch14.18 --MAb LL2-I-131 - Immunomedics MAb CH14.18-GM-CSF fusion protein --MAb LL2-Y-90 Lexigen MAb LS2D617 - Hybritech MAb chCE7 MAb LYM-1-gelonin conjugate MAb CI-137 -- AMRAD MAb LYM-1-I-131 MAb cisplatin conjugate MAb LYM-1-Y-90 MAb CLB-CD19 MAb LYM-2 -- Peregrine MAb CLB-CD19v MAb M195 MAb CLL-1 -- Peregrine MAb M195-bismuth 213 conjugate -MAb CLL-1-GM-CSF conjugate Protein Design Labs MAb M195-gelonin conjugate MAb CLL-1-IL-2 conjugate -- Peregrine MAb CLN IgG -- doxorubicin conjugates MAb M195-I-131 MAb conjugates - Tanox MAb M195-Y-90 MAb D612 MAb MA 33H1 - Sanofi MAh Dal B02 MAb MAD11 MAb DC101 - ImClone MAb MGb2 MAb MINT5 MAb EA 1 --MAb EC708 -- Biovation MAb MK2-23 MAb MOC31 ETA(252-613) conjugate MAb EP-5C7 -- Protein Design Labs MAb ERIC-1 -- ICRT MAb MOC-31-In-111 MAb F105 gene therapy MAb MOC-31-PE conjugate MAb MR6 -MAb FC 2.15 MAb MRK-16 - Aventis Pasteur MAb G250 -- Centocor MAh MS11G6 MAb GA6 MAb MX-DTPA BrE-3 MAb GA733 MAb Gliomab-H -- Viventia Biotech MAb MY9 MAb HB2-saporin conjugate MAb Nd2 -- Tosoh MAb NG-1 -- Hygeia MAb HD 37 -MAb HD37-ricin chain-A conjugate MAb NM01 - Nissin Food MAb HNK20 -- Acambis MAb OC 125 MAb OC 125-CMA conjugate MAb huN901-DM1 conjugate --MAb OKI-1 -- Ortho-McNeil ImmunoGen MAb I-131 CC49 -- Corixa MAb OX52 -- Bioproducts for Science MAb PMA5 MAb ICO25 MAb ICR12-CPG2 conjugate MAb PR1 MAb ICR-62 MAb prost 30 MAb IRac-ricin A conjugate MAb R-24 MAb K1 MAb R-24 a Human GD3 -- Celltech MAb KS1-4-methotrexate conjugate MAb RFB4-ricin chain A conjugate MAb L6 -- Bristol-Myers Squibb, Oncogen MAb RFT5-ricin chain A conjugate MAb LiCO 16-88 MAb SC 1

FIG. 28T

Muc-1 vaccine -- Corixa MAb SM-3 -- ICRT mucosal tolerance -- Aberdeen MAb SMART 1D10 -- Protein Design Labs MAb SMART ABI, 364 - Novartis mullerian inhibiting subst muplestim - Genetics Institute, Novartis, MAb SN6f MAb SN6f-deglycosylated ricin A chain DSM Anti-Infectives murine MAb - KS Biomedix conjugate -Mutant somatropin -- JCR Pharmaceutical MAb SN6i MV 833 -- Toagosei MAb SN7-ricin chain A conjugate MAb T101-Y-90 conjugate - Hybritech Mycoplasma pulmonis vaccine Mycoprex - XOMA MAb T-88 -- Chiron MAb TB94 -- Cancer ImmunoBiology myeloperoxidase - Henogen myostatin -- Genetics Institute MAb TEC 11 Nacolomab tafenatox -- Pharmacia MAb TES-23 -- Chugai MAb TM31 -- Avant Nagrecor -- Scios nagrestipen -- British Biotech MAb TNT-1 -- Cambridge Antibody Tech., NAP-5 - Corvas Intl. Peregrine NAPc2 - Corvas Intl. MAb TNT-3 MAb TNT-3 -- IL2 fusion protein -nartograstim -- Kyowa Natalizumab -- Protein Design Labs MAb TP3-At-211 Nateplase - NIH, Nihon Schering MAb TP3-PAP conjugate nateplase -- Schering AG MAb UJ13A -- ICRT NBI-3001 -- Neurocrine Biosci. MAb UN3 NBI-5788 -- Neurocrine Biosci. MAb ZME-018-gelonin conjugate NBI-6024 - Neurocrine Biosci. MAh-BC2 - GlaxoSmithKline Nef inhibitors -- BRI MAb-DM1 conjugate -- ImmunoGen Neisseria gonorrhoea vaccine -- Antex MAb-ricin-chain-A conjugate -- XOMA Biologics MAb-temoporfin conjugates Neomycin B-arginine conjugate Monopharm C -- Viventia Biotech Nerelimomab -- Chiron monteplase -- Eisai Nerve growth factor - Amgen - Chiron, montirelin hydrate - Gruenenthal moroctocog alfa - Genetics Institute Genentech Moroctocog-alfa -- Pharmacia Nerve growth factor gene therapy nesiritide citrate -- Scios MP 4 neuregulin-2 -- CeNeS MP-121 -- Biopharm neurocan -- NYU MP-52 - Biopharm neuronal delivery system -- CAMR MRA -- Chugai Neurophil inhibitory Factor -- Corvas MS 28168 - Mitsui Chemicals, Nihon Neuroprotective vaccine - University of Schering Auckland MSH fusion toxin -- Ligand neurotrophic chimaeras -- Regeneron MSI-99 -- Genaera neurotrophic factor -- NsGene, CereMedix MT 201 - Micromet

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NeuroVax -- Immune Response neurturin - Genentech neutral endopeptidase - Genentech NGF enhancers - NeuroSearch NHL vaccine - Large Scale Biology NIP45 - Boston Life Sciences NKI-B20 NM 01 - Nissin Food NMI-139 -- NitroMed NMMP -- Genetics Institute NN-2211 - Novo Nordisk Nogain - Regeneron Nonacog alfa Norelin -- Biostar Norwalk virus vaccine NRLU 10 -- NeoRx NRLU 10 PE -- NeoRx NT-3 -- Regeneron NT-4/5 - Genentech NU 3056 NU 3076 NX 1838 - Gilead Sciences NY ESO-1/CAG-3 antigen - NIH NYVAC-7 -- Aventis Pasteur NZ-1002 - Novazyme obesity therapy -- Nobex OC 10426 -- Ontogen OC 144093 -- Ontogen OCIF - Sankyo Oct-43 -- Otsuka Odulimomab - Immunotech OK PSA - liposomal OKT3-gamma-1-ala-ala OM 991 OM 992 Omalizumab -- Genentech oncoimmunin-L -- NIH Oncolysin B - ImmunoGen Oncolvsin CD6 -- ImmunoGen Oncolvsin M -- ImmunoGen Oncolvsin S -- ImmunoGen

Oncophage -- Antigenics Oncostatin M -- Bristol-Myers Squibb OncoVax-CL -- Jenner Biotherapies OncoVax-P -- Jenner Biotherapies onercept -- Yeda onychomycosis vaccine - Boehringer Ingelheim opebecan - XOMA onioids -- Arizona Opreivekin - Genetics Institute Oregovomab -- AltaRex Org-33408 b-- Akzo Nobel Orolip DP -- EpiCept oryzacystatin OSA peptides - GenSci Regeneration osteoblast-cadherin GF -- Pharis Osteocalcin-thymidine kinase gene therapy osteogenic protein -- Curis osteopontin -- OraPharma osteoporosis peptides - integra, Telios osteoprotegerin - Amgen, SnowBrand otitis media vaccines - Antex Biologics ovarian cancer -- University of Alabama OX40-IgG fusion protein - Cantab, Xenova P 246 -- Diatide P 30 - Alfaceli p1025 - Active Biotech P-113[^] - Demegen P-16 peptide - Transition Therapeutics p43 - Ramot P-50 peptide -- Transition Therapeutics p53 + RAS vaccine - NIH, NCI PACAP(1-27) analogue paediatric vaccines -- Chiron Pafase - ICOS PAGE-4 plasmid DNA -- IDEC PAI-2 - Biotech Australia, Human **Therapeutics** Palifermin (keratinocyte growth factor) --Amgen

FIG. 28V

Palivizumab - Medimmune

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PEG-uricase -- Mountain View PAM 4 -- Merck Pegvisomant -- Genentech pamiteplase - Yamanouchi PEGylated proteins, PolyMASC -- Valentis pancreatin, Minitabs - Eurand PEGylated recombinant native human leptin Pangen -- Fournier Pantarin - Selective Genetics -- Roche Parainfluenza virus vaccine - Pharmacia. Pemtumomab Pierre Fabre Penetratin -- Cyclacel Pepscan - Antisoma paraoxanase -- Esperion parathyroid hormone - Abiogen, Korea peptide G - Peptech, ICRT peptide vaccine - NIH ,NCI Green Cross Pexelizumab Parathyroid hormone (1-34) -pexiganan acetate -- Genaera Chugai/Suntory Parkinson's disease gene therapy - Cell Pharmaprojects No. 3179 -- NYU Pharmaprojects No. 3390 - Ernest Orlando Genesys/ Ceregene Parvovirus vaccine -- Medimmune Pharmaprojects No. 3417 -- Sumitomo Pharmaprojects No. 3777 -- Acambis PCP-Scan - Immunomedics PDGF -- Chiron Pharmaprojects No. 4209 - XOMA Pharmaprojects No. 4349 - Baxter Intl. PDGF cocktail -- Theratechnologies Pharmaprojects No. 4651 peanut allergy therapy - Dynavax Pharmaprojects No. 4915 -- Avanir PEG anti-ICAM MAb -- Boehringer Pharmaprojects No. 5156 -- Rhizogenics Ingelheim Pharmaprojects No. 5200 -- Pfizer PEG asparaginase -- Enzon · Pharmaprojects No. 5215 -- Origene PEG alucocerebrosidase Pharmaprojects No. 5216 -- Origene PEG hirudin -- Knoll Pharmaprojects No. 5218 - Origene PEG interferon-alpha-2a -- Roche Pharmaprojects No. 5267 - ML PEG interferon-alpha-2b + ribavirin --Laboratories Biogen, Enzon, ICN Pharmaceuticals, Pharmaprojects No. 5373 - MorphoSys Schering-Plough Pharmaprojects No. 5493 -- Metabolex PEG MAb A5B7 -Pharmaprojects No. 5707 - Genentech Pegacaristim - Amgen - Kirin Brewery --Pharmaprojects No. 5728 - Autogen ZymoGenetics Pharmaprojects No. 5733 -- BioMarin Pegaldesleukin -- Research Corp Pharmaprojects No. 5757 - NIH pegaspargase -- Enzon Pharmaprojects No. 5765 - Gryphon pegfilgrastim -- Amgen Pharmaprojects No. 5830 - AntiCancer PEG-interferon Alpha -- Viragen Pharmaprojects No. 5839 -- Dyax PEG-interferon Alpha 2A -- Hoffman La-Pharmaprojects No. 5849 -- Johnson & Johnson PEG-interferon Alpha 2B -- Schering-Pharmaprojects No. 5860 -- Mitsubishi-Plough PEG-r-hirudin -- Abbott Tokyo PEG-rHuMGDF -- Amgen

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prostate-specific antigen -- EntreMed RD 62198 protein A -- RepliGen rDnase -- Genentech protein adhesives - Enzon RDP-58 -- SangStat protein C -- Baxter Intl., PPL Therapeutics. RecepTox-Fce - Kervx RecepTox-GnRH - Keryx, MTR ZvmoGenetics Technologies protein C activator - Gilead Sciences RecepTox-MBP - Keryx, MTR protein kinase R antags -- NIH protirelin - Takeda Technologies recFSH - Akzo Nobel, Organon protocadherin 2 - Caprion Pro-urokinase - Abbott, Bristol-Myers REGA 3G12 Regavirumab - Teilin Squibb, Dainippon, Tosoh - Welfide P-selectin glycoprotein ligand-1 - Genetics relaxin - Connetics Corp Renal cancer vaccine - Macropharm Institute pseudomonal infections -- InterMune repifermin - Human Genome Sciences Pseudomonas vaccine - Cytovax Respiratory syncytial virus PFP-2 vaccine --PSGL-Ig -- American Home Products Wyeth-Lederle PSP-94 -- Procvon Respiratory syncytial virus vaccine --GlaxoSmithKline, Pharmacia, Pierre Fabre PTH 1-34 -- Nobex Respiratory syncytial virus vaccine Outlimmune-M - Antigenics inactivated R 744 -- Roche Respiratory syncytial virus-parainfluenza R 101933 R 125224 -- Sankyo virus vaccine -- Aventis Pasteur. Pharmacia RA therapy - Cardion Rabies vaccine recombinant -- Aventis Reteplase - Boehringer Mannheim, Pasteur, BioChem Vaccines, Kaketsuken Hoffman La-Roche Retropep -- Retroscreen Pharmaceuticals RadioTheraClM - YM BloSciences RFB4 (dsFv) PE38 Ramot project No. 1315 -- Ramot RFI 641 - American Home Products RFTS - UAB Research Foundation Ramot project No. K-734A -- Ramot Ramot project No. K-734B -- Ramot RG 12986 -- Aventis Pasteur RG 83852 -- Aventis Pasteur Ranibizumab (Anti-VEGF fragment) --Genentech RG-1059 - RepliGen RANK -- Immunex rGCR -- NIH ranpirnase -- Alfacell rGLP-1 -- Restoragen ranpirnase-anti-CD22 MAb -- Alfacell rGRF -- Restoragen RANTES inhibitor - Milan rh Insulin - Eli Lilly RAPID drug delivery systems - ARIAD RHAMM targeting peptides - Cangene rasburicase -- Sanofi rHb1.1 - Baxter Intl. rhCC10 - Claragen rBPI-21, topical -- XOMA RC 529 -- Corixa rhCG - Serono · rCFTR - Genzyme Transgenics Rheumatoid arthritis gene therapy

FIG. 28Y

Rheumatoid arthritis vaccine - Veterans SB RA 31012 -SC 56929 - Pharmacia Affairs Medical Center SCA binding proteins - Curis, Enzon rhl.H -- Serono scFv(14E1)-ETA Berlex Laboratories, Ribozyme gene therapy - Genset Rickettsial vaccine recombinant Schering AG ScFv(FRP5)-ETA -RIGScan CR -- Neoprobe ScFv6C6-PE40 -RIP-3 -- Rigel SCH 55700 -- Celltech Rituximab -- Genentech Schistosomiasis vaccine -- Glaxo RK-0202 -- RxKinetix Wellcome/Medeva, Brazil RLT peptide -- Esperion SCPF - Advanced Tissue Sciences rM/NEI -- IVAX scuPA-suPAR complex - Hadasit rmCRP -- Immtech SD-9427 -- Pharmacia RN-1001 -- Renovo SDF-1 -- Ono RN-3 -- Renovo SDZ 215918 - Novartis RNAse conjugate -- Immunomedics SDZ 280125 - Novartis RO 631908 -- Roche SDZ 89104 -- Novartis Rotavirus vaccine - Merck SDZ ABL 364 -- Novartis RP 431 -- DuPont Pharmaceuticals SDZ MMA 383 -- Novartis RP-128 -- Resolution Secretin - Ferring, Replicen RPE65 gene therapy -serine protease inhibs -- Pharis RPR 110173 -- Aventis Pasteur sermorelin acetate - Serono RPR 115135 -- Aventis Pasteur SERP-1 -- Viron RPR 116258A -- Aventis Pasteur sertenef -- Dainippon rPSGL-Ig -- American Home Products serum albumin, Recombinant human r-SPC surfactant - Byk Gulden RSV antibody -- Medimmune Aventis Behring serum-derived factor -- Hadasit Ruplizumab -- Biogen Sevirumab -- Novartis rV-HER-2/neu - Therion Biologics SGN 14 - Seatle Genetics SA 1042 -- Sankvo SGN 15 - Seatle Genetics sacrosidase - Orphan Medical SGN 17/19 - Seatle Genetics SGN 30 - Seatle Genetics Sargramostim -- Immunex SGN-10 - Seatle Genetics saruplase -- Gruenenthal SGN-11 -- Seatle Genetics Satumomab -- Cytogen SH 306 - DuPont Pharmaceuticals SB 1 - COR Therapeutics Shanvac-B -- Shantha SB 207448 -- GlaxoSmithKline Shigella flexneri vaccine - Avant, Acambis, SB 208651 - GlaxoSmithKline Novavax SB 240683 -- GlaxoSmithKline SB 249415 -- GlaxoSmithKline Shigella sonnei vaccine sICAM-1 - Boehringer Ingelheim SB 249417 -- GlaxoSmithKline Silteplase - Genzyme SB 6 -- COR Therapeutics

FIG. 28Z

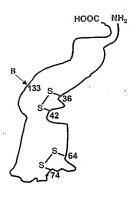
Staphylococcus aureus vaccine conjugate --SIV vaccine - Endocon, Institut Pasteur SK 896 - Sanwa Kagaku Kenkyusho SK-827 - Sanwa Kagaku Kenkyusho Staphylococcus therapy -- Tripep Staphylokinase - Biovation, Prothera, Skeletey -- CellFactors SKF 106160 - GlaxoSmithKline Thrombogenetics Streptococcal A vaccine - M6 S-nitroso-AR545C -Pharmaceuticals, North American Vaccine SNTP -- Active Biotech Streptococcal B vaccine -- Microscience somatomedin-1 -- GroPep, Mitsubishi-Streptococcal B vaccine recombinant --Tokyo, NIH Biochem Vaccines somatomedin-1 carrier protein -- Insmed Streptococcus pyogenes vaccine somatostatin -- Ferring STRL-33 -- NIH Somatotropin/ Subalin -- SRC VB VECTOR Human Growth Hormone -- Bio-Tech. SUIS - United Biomedical General, Eli Lilly somatropin -- Bio-Tech. General, Alkermes, SUIS-LHRH -- United Biomedical ProLease, Aventis Behring, Biovector, SUN-E3001 - Suntory super high affinity monoclonal antibodies --Cangene, Dong-A, Eli Lilly, Emisphere, Enact, Genentech, Genzyme Transgenics, YM BloSciences Grandis/InfilMed, CSL, InfilMed, MacroMed, Superoxide dismutase - Chiron, Enzon, Ube Industries, Bio-Tech, Yeda Novartis, Novo Nordisk, Pharmacia superoxide dismutase-2 -- OXIS Serono, TranXenoGen suppressin - UAB Research Foundation somatropin derivative - Schering AG SY-161-P5 - ThromboGenics somatropin, AIR -- Eli Lilly Somatropin, inhaled - Eli Lilly/Alkermes SY-162 -- ThromboGenics Systemic lupus erythematosus vaccine -somatropin, Kabl -- Pharmacia MedClone/VIvoRx somatropin, Orasome - Novo Nordisk Sonermin -- Dainippon Pharmaceutical T cell receptor peptides -- Xoma T cell receptor peptide vaccine SP(V5.2)C - Supertek T4N5 liposomes -- AGI Dermatics SPf66 TACI, soluble - ZymoGenetics sphingomyelinase - Genzyme targeted apoptosis - Antisoma SR 29001 - Sanofi tasonermin -- Boehringer Ingelheim SR 41476 - Sanofi TASP SR-29001 - Sanofi TASP-V SS1(dsFV)-PE38 - NeoPharm Tat peptide analogues -- NIH ß2 microglobulin -- Avidex ß2-microglobulin fusion proteins -- NIH TBP I -- Yeda TBP II ß-amyloid peptides -- CeNeS TBV25H -- NIH ß-defensin -- Pharis Tc 99m ior cea1 - Center of Molecular Staphylococcus aureus infections --Immunology Inhibitex/ZLB Tc 99m P 748 -- Diatide

FIG. 28AA

Tissue factor - Genentech Tc 99m votumumab - Intracell Tissue factor pathway inhibitor Tc-99m rh-Annexin V - Theseus Imaging T.JN-135 -- Tsumura teceleukin -- Biogen TM 27 - Avant tenecteplase - Genentech Teriparatide -- Armour Pharmaceuticals, TM 29 - Avant Asahi Kasei, Eli Lilly TMC-151 - Tanabe Seiyaku TNF tumour necrosis factor -- Asahi Kasei terlipressin - Ferring testisin -- AMRAD TNF Alpha - Cytimmune TNF antibody -- Johnson & Johnson Tetrafibricin -- Roche TNF binding protein - Amgen TFPI -- EntreMed TNF degradation product - Oncotech toD-IL-2 - Takeda TNF receptor - Immunex TGF-Alpha -- ZymoGenetics TNF receptor 1, soluble -- Amgen TGF-ß -- Kolon TNF Tumour necrosis factor-alpha - Asahi TGF-82 -- Insmed TGF-ß3 -- OSI Kasel, Genetech, Mochida Thalassaemia gene therapy - Crucell TNF-Alpha Inhibitor -- Tripep TNFR:Fc gene therapy - Targeted Genetics TheraCIM-h-R3 -- Center of Molecular Immunology, YM BioSciences TNF-SAM2 Theradigm-HBV -- Epimmune ToleriMab - Innogenetics Theradigm-HPV -- Epimmune Toxoplasma gondii vaccine --GlaxoSmithKline Theradigm-malaria -- Epimmune TP 9201 - Telios Theradigm-melanoma - Epimmune TheraFab -- Antisoma TP10 - Avant TP20 -- Avant ThGRF 1-29 -- Theratechnologies tPA -- Centocor ThGRF 1-44 -- Theratechnologies trafermin -- Scios Thrombin receptor activating peptide ---TRAIL/Apo2L -- Immunex Abbott TRAIL-R1 MAb - Cambridge Antibody thrombomodulin - Iowa, Novocastra Thrombopoietin - Dragon Pharmaceuticals, Technologies transferrin-binding proteins - CAMR Genentech thrombopoletin, Pliva -- Receptron Transforming growth factor-beta-1 -Thrombospondin 2 -Genentech transport protein -- Genesis thrombostatin - Thromgen Trastuzumab -- Genetech thymalfasin - SciClone TRH -- Ferring thymocartin - Gedeon Richter Triabin - Schering AG thymosin Alpha1 - NIH Triconal · thyroid stimulating hormone - Genzyme Triflavin tlCAM-1 -- Baver troponin I - Boston Life Sciences Tick anticoagulant peptide - Merck TRP-24 -- NIH TIF - Xoma trypsin inhibitor - Mochida Tifacogin -- Chiron, NIS, Pharmacia

FIG. 28BB

Vascular endothelial growth factors - R&D TSP-1 gene therapy -TT-232 vascular targeting agents - Peregrine TTS-CD2 -- Active Biotech vasopermeation enhancement agents --Tuberculosis vaccine - Aventis Pasteur. Peregrine Genesis vasostatin -- NIH Tumor Targeted Superantigens - Active VCL -- Bio-Tech, General Biotech - Pharmacia VEGF - Genentech, Scios turnour vaccines - PhotoCure tumour-activated prodrug antibody VEGF inhibitor -- Chugai VEGF-2 - Human Genome Sciences conjugates - Millennium/ImmunoGen VFGF-Trap -- Regeneron tumstatin -- ILEX viscumin, recombinant - Madaus Tuvirumab -- Novartis Vitaxin TV-4710 - Teva Vitrase -- ISTA Pharmaceuticals TWEAK receptor -- Immunex West Nile virus vaccine -- Bavarian Nordic TXU-PAP WP 652 TY-10721 - TOA Eivo Type I diabetes vaccine - Research Corp WT1 vaccine -- Corixa WX-293 - Wllex BioTech. Typhoid vaccine CVD 908 WX-360 -- Wilex BioTech. U 143677 -- Pharmacia WX-UK1 -- Wilex BioTech. U 81749 - Pharmacia XMP-500 -- XOMA UA 1248 -- Arizona XomaZyme-791 -- XOMA UGIF - Sheffield XTL 001 - XTL Biopharmaceuticals UIC 2 XTL 002 - XTL Biopharmaceuticals UK 101 veast delivery system -- Globelmmune UK-279276 -- Corvas Intl. Yersinia pestis vaccine urodilatin -- Pharis YIGSR-Stealth - Johnson & Johnson urofollitrophin - Serono Yissum Project No. D-0460 -- Yissum Urokinase -- Abbott YM 207 - Yamanouchl uteroferrin-- Pepgen YM 337 -- Protein Design Labs V 20 – GLYCODesign Yttrium-90 labelled biotin V2 vasopressin receptor gene therapy Yttrium-90-labeled anti-CEA MAb T84.66 vaccines -- Active Biotech ZD 0490 – AstraZeneca Varicella zoster glycoprotein vaccine -ziconotide -- Elan Research Corporation Technologies Varicella zoster virus vaccine live - Cantab ZK 157138 - Berlex Laboratories Zolimomab aritox Pharmaceuticals 5 3 2 2 Zorcell -- Immune Response Vascular endothelial growth factor -Genentech, University of California ZRXL peptides -- Novartis



$$\mathbf{B} \leftarrow \begin{pmatrix} (\operatorname{Sia})_{b} \\ -\operatorname{GalNAc-(Gal)}_{a} - (\operatorname{Sia})_{c} - (R)_{d} \end{pmatrix}_{e}$$

a-c, e (independently selected) = 0 or 1; d = 0; R = modifying group, sialyl or oligosialyl

FIG. 29A

CHO, BHK, 293 cells, Vero expressed G-CSF a-c, e (independently selected) = 0 or 1; d = 0

1. Sialidase 2. CMP-SA-PEG, ST3Gal1

a-d, e (independently selected) = 0 or 1; R = PEG.

FIG. 29B

Insect cell expressed G-CSF

a, e (independently selected) = 0 or 1; b, c, d = 0.

1. Galactosyltransferase, UDP-Gal
2. CMP-SA-PEG, ST3Gal1

a, c, d, e (independently selected) = 0 or 1; R = PEG.

FIG. 29C

E. coli expressed G-CSF a-e = 0.

1. GalNAc Transferase, UDP-GalNAc

2. CMP-SA-PEG, sialyltransferase

c, d, e (independently selected) = 0 or 1; a, b = 0; R = PEG.

FIG. 29D

NSO expressed G-CSF a, e (independently selected) = 0 or 1;

1. CMP-SA-levulinate, ST3Gal1

b=0; R=PEG.

b, c, d = 0

▼ 2. H₄N₂-PEG
 a, c, d, e (independently selected) = 0 or 1;

· FIG. 29E

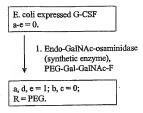


FIG. 29F

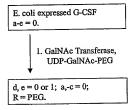
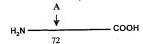


FIG. 29G



$$\mathbf{A} \leftarrow \begin{bmatrix} [\operatorname{GlcNAc-(Gal)}_{a}]_{a}^{-} \cdot (\operatorname{Sia})_{j}^{-} \cdot (R)_{v} \\ - \operatorname{GlcNAc-GlcNAc-Man} \\ \operatorname{Man} \begin{bmatrix} [\operatorname{GlcNAc-(Gal)}_{b}]_{r}^{-} \cdot (\operatorname{Sia})_{k}^{-} \cdot (R)_{w} \\ \\ [\operatorname{GlcNAc-(Gal)}_{b}]_{r}^{-} \cdot (\operatorname{Sia})_{k}^{-} \cdot (R)_{w} \end{bmatrix}_{t} \\ \operatorname{Man} \begin{bmatrix} [\operatorname{GlcNAc-(Gal)}_{d}]_{a}^{-} \cdot (\operatorname{Sia})_{j}^{-} \cdot (R)_{w} \\ \\ [\operatorname{GlcNAc-(Gal)}_{d}]_{h}^{-} \cdot (\operatorname{Sia})_{m}^{-} \cdot (R)_{y} \end{bmatrix}_{t} \\ \operatorname{Man} \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{d} \\ \\ \operatorname{GlcNAc-(Gal)}_{d} \\ \end{bmatrix}_{t}^{-} \cdot (\operatorname{Sia})_{j}^{-} \cdot (R)_{w} \end{bmatrix}_{t} \\ \operatorname{Man} \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{d} \\ \\ \operatorname{GlcNAc-(Gal)}_{d} \\ \\ \operatorname{GlcNAc-(Gal)}_{d} \\ \end{bmatrix}_{t}^{-} \cdot (\operatorname{Sia})_{j}^{-} \cdot (R)_{w} \end{bmatrix}_{t} \\ \operatorname{Man} \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{d} \\ \\ \operatorname{GlcNAc-(Gal)}_{d$$

a-d, i, n-u (independently selected) = 0 or 1. aa, bb, cc, dd, ee (independently selected) = 0 or 1. c-h (independently selected) = 0 to 6. j-m (independently selected) = 0 to 20. v-z=0; R = modifying group, mamnose, oligo-mannose. R'=H, glycosyl residue, modifying group, glycoconjugate.

FIG. 30A

```
GIO, BHK, 293 cells, Vero expressed interferon alpha 14C. a-d, aa, bb = 1; e-h = 1 to 4; cc, j-m, i, r-u (independently selected) = 0 or 1; q, n-p, v-z, cc, dd, ee = 0.
```

```
1. Sialidase
```

2. CMP-SA-PEG, ST3Gal3

```
a-d, aa, bb = 1; e-h = 1 to 4;
bb, cc, i, r-u (independently selected) = 0 or 1;
q, n-p, v-z, cc, dd, ee = 0;
v-y (independently selected) = 1,
when j-m (independently selected) = 1;
R = PEG.
```

FIG. 30B

```
Insect cell or fungi expressed interferon alpha-14C. a-d, f, h, j-q, s, u, v-z, cc, dd, ee = 0; e, g, i, r, t (independently selected) = 0 or 1; aa, bb = 1.
```

```
1. GNT's 1&2, UDP-GlcNAc
2. Galactosyltransferase, UDP-Gal-PEG
```

```
b, d, f, h, j-q, s, u, w, y, z, cc, dd, ee = 0;

a, c, e, g, i, r, t, v, x (independently selected) = 0 or 1;

v, x (independently selected) = 1,

when a, c, (independently selected) = 1;

aa, bb = 1; R = PEG.
```

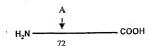
FIG. 30C

Yeast expressed interferon alpha-14C. a-q, cc, dd, ee, v-z=0; r-y (independently selected) = 0 to 1; aa, bb = 1; R (branched or linear) = Man, oligomannose or polysaccharide.

- 2. Galactosyltransferase, UDP-Gal 3.. CMP-SA-PEG, ST3Gal3

a-z, bb = 0; aa = 1; R' = -Gal-Sia-PEG.

FIG. 30D



$$(Fuc)_{i} \\ - GicNAc \\ - GicNAc$$

a-d, i, r-u (independently selected) = 0 or 1. e-h (independently selected) = 0 to 4. j-m (independently selected) = 0 or 1. n, v-y = 0; z = 0 or 1. R = polymer; R' = sugar, glycoconjugate.

FIG. 30E

```
CHO, BHK, 293 cells, Vero expressed interferon alpha-14C.

h = 1 to 3;
a-g, j-m, i (independently selected) = 0 or 1;
r-u (independently selected) = 0 or 1;
n, v-y = 0; z = 1.
```

1. CMP-SA-PEG, ST3Gal3

```
h=1 to 3;
a-g, i (independently selected) = 0 or 1;
r-u (independently selected) = 0 or 1;
j-m, v-y (independently selected) = 0 or 1;
z=1; n=0; R=PEG.
```

FIG. 30F

```
Insect cell or fungi expressed interferon alpha-14C. a-d, f, h, j-n, s, u, v-y = 0; e, g, i, r, t (independently selected) = 0 or 1; z=1.
```

```
    GNT's 1,2,4,5, UDP-GlcNAc
    Galactosyltransferase, UDP-Gal
```

3. CMP-SA-PEG, ST3Gal3

a-m, r-y (independently selected) = 0 or 1; z=1; n=0; R=PEG.

FIG. 30G

Yeast expressed interferon alpha-14C. a-n = 0; r-y (independently selected) = 0 to 1; z = 1; R (branched or linear) = Man, oligomannose.

- 1. mannosidases
- 2. GNT's 1.2,4.5, UDP-GlcNAc
- 3. Galactosyltransferase, UDP-Gal
- ↓ 4.. CMP-SA-PEG, ST3Gal3

a-m, r-y (independently selected) = 0 or 1; z = 1; n = 0; R = PEG.

FIG. 30H

NSO expressed interferon alpha 14C. a-i, r-u (independently selected) = 0 or 1; j-m, n, v-y = 0; z = 1.

> CMP-SA-levulinate, ST3Gal3, buffer, salt
> H₄N₇-PEG

a-i, j-m, r-y (independently selected) = 0 or 1; n = 0; z = 1; R = PEG.

FIG. 301

CHO, BHK, 293 cells, Vero expressed interferon alpha-14C.
h = 1 to 3;
a-g, j-m, i (independently selected) = 0 or 1;
ru (independently selected) = 0 or 1;
n, v-y = 0; z = 1.

1. CMP-SA-PEG, α2,8-ST

h=1 to 3; a-g, i, r-u (independently selected) = 0 or 1; j-m (independently selected) = 0 to 2; v-y (independently selected) = 1, when j-m (independently selected) is 2; z=1; n=0; R=PEG.

FIG. 30J

CHO, BHK, 293 cells, Vero expressed
Interferon alpha-14C.
a-g, j-m, r-u (independently selected) = 0 or 1;
h = 1 to 3; n, v-y = 0; z = 1.

- Sialidase
 Trans-sialidase, PEG-Sia-lactose
- a-g, j-m, r-y (independently selected) = 0 or 1; h = 1 to 3; n = 0; z = 1; R = PEG.

FIG. 30K

CHO, BHK, 293 cells, Vero expressed interferon alpha-14C. $h=1\ to\ 3;$ a-g, j-m, i (independently selected) = 0 or 1; r-u (independently selected) = 0 or 1; n, v-y = 0; z = 1.

1. CMP-SA, α2,8-ST

h=1 to 3; a-g, i, r-u (independently selected) = 0 or 1; j-m (independently selected) = 0 to 40; z=1; v-y, n=0.

FIG. 30L

Insect cell or fungi expressed interferon alpha-14C. a-d, f, h, j-n, s, u, v-y = 0; e, g, i, r, t (independently selected) = 0 or 1; z = 1.

- GNT's 1 & 2, UDP-GlcNAc
 Galactosyltransferase,
 UDP-Gal-linker-SA-CMP
- 3. ST3Gal3, transferrin

a, c, e, g, i, r, t, v, x (independently selected) = 0 or 1; z=1; b, d, f, h, j-n, s, u, w, y=0; R= transferrin.

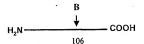
FIG. 30M

Insect cell or fungi expressed interferon alpha-14C. a-d, f, h, j-n, s, u, v-y = 0; e, g, i, r, t (independently selected) = 0 or 1; z = 1.

- 1. endoglycanase
- 2. Galactosyltransferase, UDP-Gal-linker-SA-CMP
- 3. ST3Gal3, transferrin

```
 \begin{array}{l} i \; (independently \; selected) = 0 \; or \; 1; \\ a-h, \; j-m, \; r-z=0; \\ n=1; \; R'=-Gal-linker-transferrin. \end{array}
```

FIG. 30N



$$\begin{array}{c} \left(\begin{array}{c} (GlcNAc-Gal)_{\underline{\Gamma}}(Sia)_{b^{-}}(R)_{g} \\ -GalNAc-(Gal)_{a^{-}}(Sia)_{c^{-}}(R)_{d} \end{array} \right) \end{array}$$

a-c, e, f (independently selected) = 0 or 1; d, g = 0; R = polymer, glycoconjugate.

FIG. 300

CHO, BHK, 293 cells, Vero expressed IF-alpha (2a or 2b). a-c (independently selected) = 0 or 1; e=1; d, f, g=0

1, Sialidase 2, CMP-SA-PEG, ST3Gall

a-d (independently selected) = 0 or 1; e = 1; b, f, g = 0; R = PEG.

FIG. 30P

Insect cell expressed interferon alpha (2a or 2b). a, e (independently selected) = 0 or 1; b, c, d, f, g = 0.

Galactosyltransferase, UDP-Gal
 CMP-SA-PEG, ST3Gal1

a, c, d, e (independently selected) = 0 or 1; b, f, g = 0; R = PEG.

FIG. 30Q

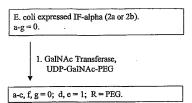


FIG. 30R

```
NSO expressed IF-alpha (2a or 2b).
a (independently selected) = 0 or 1;
e = 1; b, c, d, f, g = 0

1. CMP-SA-levulinate, ST3Gall
2. H_4N_2-PEG

a, c, d (independently selected) = 0 or 1;
e = 1; b, f, g = 0; R = PEG.
```

FIG. 30S

E. coli expressed IF-alpha (2a or 2b). a-g = 0.

 Endo-N-acetylgalatosamidase (synthetic enzyme),
 PEG-Gal-GalNAc-F

a, d, e = 1; b, c, f, g = 0; R = PEG.

FIG. 30T

E. coli expressed IF-alpha (2a or 2b). a-g = 0.

- 1. GalNAc Transferase, UDP-GalNAc
- 2. sialyltransferase, CMP-SA-PEG

b, d = 0 or 1; e = 1; a, c, f, g = 0; R = PEG.

--- ----

FIG. 30U

```
CHO, BHK, 293 cells, Vero expressed IF-alpha (2a or 2b). a-c, f (independently selected) = 0 or 1; e=1; d, g=0
```

Sialidase
 CMP-SA-PEG, ST3Gal1 and ST3Gal3

a-d, f, g (independently selected) = 0 or 1; e = 1; R = PEG.

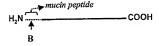
FIG. 30V

```
CHO, BHK, 293 cells, Vero expressed IF-alpha (2a or 2b). a-c, f (independently selected) = 0 or 1; e = 1; d, g = 0
```

- 1. Sialidase
 2. CMP-SA-linker-SA-CMP,
 ,ST3Gal1
 3. ST3Gal3, transferrin
- a-d, f (independently selected) = 0 or 1; e = 1; R = transferrin; g = 0.

FIG. 30W





$$\mathbf{B} \leftarrow \begin{bmatrix} (\operatorname{Sia})_{b} \\ -\operatorname{GalNAc-(Gal)}_{a} - (\operatorname{Sia})_{c} - (\mathbb{R})_{d} \end{bmatrix}_{c}$$

a-c, e (independently selected) = 0 or 1; d=0; R= polymer, glycoconjugate.

FIG. 30X

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CHO, BHK, 293 cells, Vero expressed interferon alpha-mucin fusion protein. a-c, e (independently selected) = 0 or 1; d=0

Sialidase
 CMP-SA-PEG, ST3Gal1

a-d, e (independently selected) = 0 or 1; R = PEG.

FIG. 30Y

Insect cell expressed interferon alpha-mucin fusion protein.

a, e (independently selected) = 0 or 1;

a, e (independently selected) = 0 or 1 b, c, d = 0.

1. Galactosyltransferase, UDP-Gal-PEG

a, d, e (independently selected) = 0 or 1; b, c = 0; R = PEG.

FIG. 30Z

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E. coli expressed interferon alpha-mucin fusion protein.

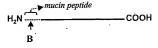
a-e = 0.

GalNAc Transferase, UDP-GalNAc
 CMP-SA-PEG, sialyltransferase

c, d, e (independently selected) = 0 or 1; a, b = 0; R = PEG.

FIG. 30AA





$$\mathbf{B} \quad \blacktriangleleft \begin{bmatrix} (\mathrm{Sia})_b \\ \cdot \\ -\mathrm{GalNAc\text{-}(Gal)_a\text{-}}(\mathrm{Sia})_c\text{-} (\mathbb{R})_d \end{bmatrix}_c$$

a-c, e (independently selected) = 0 or 1; d = 0; R = polymer, linker.

FIG. 30BB

E. coli expressed interferon alpha-mucin fusion protein.

a-e, n=0.

 GalNAc Transferase, UDP-GalNAc-PEG

d, e (independently selected) = 0 or 1; a-c, n = 0; R = PEG.

FIG. 30CC

.

E. coli expressed interferon alpha-mucin fusion protein.

a-e, n = 0.

- GalNAc Transferase,
 UDP-GalNAc-linker-SA-CMP
 ST3Gal3, asialo-transferrin
 - 3. CMP-SA, ST3Gal3

d, e (independently selected) = 0 or 1; a-c, n = 0; R = linker-transferrin.

FIG. 30DD

E. coli expressed Interferon alpha (no fusion). a-e, $\mathbf{n}=\mathbf{0}$.

NHS-CO-linker-SA-CMP
 ST3Gal3, transferrin

a-e = 0; n = 1; R' = linker-transferrin.

FIG. 30EE



$$(\operatorname{Fuc})_{j} = \left(\operatorname{GlcNAc-(Gal)}_{a} \right)_{e} - (\operatorname{Sia})_{g} - (\operatorname{R})_{v} \right)_{g} = \left(\operatorname{GlcNAc-(Gal)}_{a} \right)_{e} - (\operatorname{Sia})_{g} - (\operatorname{R})_{v} \right)_{g} = \left(\operatorname{GlcNAc-(Gal)}_{b} \right)_{e} - (\operatorname{Sia})_{g} - (\operatorname{R})_{v} \right)_{g} = \left(\operatorname{GlcNAc-(Gal)}_{b} \right)_{g} - (\operatorname{Sia})_{g} - (\operatorname{R})_{v} \right)_{g} = \left(\operatorname{GlcNAc-(Gal)}_{b} \right)_{g} - (\operatorname{Sia})_{g} - (\operatorname{R})_{v} \right)_{g} = \left(\operatorname{GlcNAc-(Gal)}_{b} \right)_{g} - (\operatorname{Sia})_{g} - (\operatorname{R})_{v} \right)_{g} = \left(\operatorname{GlcNAc-(Gal)}_{b} \right)_{g} - (\operatorname{Sia})_{g} - (\operatorname{R})_{g} \right)_{g} = \left(\operatorname{Sia})_{g} - (\operatorname{R})_{g} \right)_{g} = \left(\operatorname{R})_{g} - (\operatorname{R})_{g} \right)_{g} = \left(\operatorname{R})_{g} - (\operatorname{R})_{g} \right)_{g} = \left(\operatorname{R})_{g} - (\operatorname{R})_{g} - (\operatorname{R})_{g} \right)_{g} = \left(\operatorname{R})_{g} - (\operatorname{R})_{g} - (\operatorname{R})_{g} \right)_{g} = \left(\operatorname{R})_{g} - (\operatorname{R})_{g} - (\operatorname{R})_{g} - (\operatorname{R})_{g} - (\operatorname{R})_{g} \right)_{g} = \left(\operatorname{R})_{g} - (\operatorname{R})_{g} - (\operatorname{R})_{$$

a-d, i, r-u (independently selected) = 0 or 1. e-h (independently selected) = 0 to 4. j-m (independently selected) = 0 or 1. n, v-y = 0; z = 0 or 1; R = polymer

FIG. 31A

CHO, BHK, 293 cells, Vero expressed IF-beta h=1 to 3; a-g, j-m, i (independently selected) = 0 or 1; r-u (independently selected) = 0 or 1; n, v-y = 0; z = 1.

Sialidase
 CMP-SA-PEG, ST3Gal3

h = 1 to 3; a = g, i (independently selected) = 0 or 1; r = u (independently selected) = 0 or 1; j = m, v = y (independently selected) = 0 or 1; j = z = 1; j = 0; j = 0 PEG.

FIG. 31B

Insect cell expressed IF-beta a-d, f, h, j-n, s, u, v-y = 0; e, g, i, r, t (independently selected) = 0 or 1; z = 1.

 GNT's 1&2, UDP-GlcNAc
 Galactosyltransferase, UDP-Gal
 CMP-SA-PEG, ST3Gal3, buffer, salt

b, d, f, h, k, m, n, s, u, w, y = 0; a, c, e, g, i, r, t (independently selected) = 0 or 1; j, l, v, x (independently selected) = 0 or 1; z = 1; R = PEG.

FIG. 31C

Yeast expressed IF-beta a-n = 0; z = 1; r-y (independently selected) = 0 to 1; R (branched or linear) = Man, oligomannose or polysaccharide.

1. Endo-H
2. Galactosyltransferase, UDP-Gal
3.. CMP-SA-PEG, ST3Gal3

a-m, r-z=0; n = 1; R' = -Gal-Sia-PEG.

FIG. 31D

CHO, BHK, 293 cells, Vero expressed IF-beta h=1 to 3; a-g, j-m, i (independently selected) = 0 or 1; r-u (independently selected) = 0 or 1; n, v-y=0; z=1.

1. CMP-SA-PEG, ST3Gal3

 $\begin{array}{l} h=1 \text{ to 3;} \\ a-g, i \text{ (independently selected)} = 0 \text{ or 1;} \\ r-u \text{ (independently selected)} = 0 \text{ or 1;} \\ j-m, v-y \text{ (independently selected)} = 0 \text{ or 1;} \\ z=1; \ n=0; \ R=PEG. \end{array}$

FIG. 31E

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$$\label{eq:local_local_local} \begin{split} & \text{Insect cell expressed IF-beta} \\ & \text{a-d, f, h, j-n, s, u, v-y} = 0; \text{ e, g, i, r, t} \\ & \text{(independently selected)} = 0 \text{ or 1; } z = 1. \end{split}$$

- GNT's 1,2,4,5, UDP-GlcNAc
 Galactosyltransferase, UDP-Gal
 CMP-SA-PEG, ST3Gal3
- a-m, r-y (independently selected) = 0 or 1; z=1; n=0; R=PEG.

FIG. 31F

```
Yeast expressed IF-beta

a-n = 0; z = 1;

r-y (independently selected) = 0 to 1;

R (branched or linear) = Man, oligomannose.
```

- 1. mannosidases
- 2. GNT's 1,2,4,5, UDP-GlcNAc
- 3. Galactosyltransferase, UDP-Gal 4.. CMP-SA-PEG, ST3Gal3
- a-m, r-y (independently selected) = 0 or 1; z=1; n=0; R=PEG.

```
NSO expressed IF-beta
a-i, r-u (independently selected) = 0 or 1;
j-m, n, v-y = 0; z = 1.

1. CMP-SA-levulinate, ST3Gal3,
buffer, salt
2. H<sub>4</sub>N<sub>2</sub>-PEG

a-i, j-m, r-y (independently selected) = 0 or 1;
```

n = 0; z = 1; R = PEG.

FIG. 31H

```
CHO, BHK, 293 cells, Vero expressed IF-beta h=1 to 3; a-g, j-m, i (independently selected) = 0 or 1; r-u (independently selected) = 0 or 1; n, v-y = 0; z = 1.
```

1. CMP-SA-PEG, α2,8-ST

```
h=1 to 3;
a-g, i, r-u (independently selected) = 0 or 1;
j-m (independently selected) = 0 to 2;
v-y (independently selected) = 1,
when j-m (independently selected) is 2;
z=1; n=0; R=PEG.
```

FIG. 311

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CHO, BHK, 293 cells, Vero expressed IF-beta a-g, j-m, r-u (independently selected) = 0 or 1; h=1 to 3; n, v-y = 0; z=1.

- 1. Sialidase
- 2. Trans-sialidase, PEG-Sia-lactose

a-g, j-m, r-y (independently selected) = 0 or 1; h = 1 to 3; n = 0; z = 1; R = PEG.

FIG. 31J

CHO, BHK, 293 cells, Vero expressed Ifin-beta. a-d, i-m, r-u, z (independently selected) = 0 or 1; e-h = 1; n, v-y = 0.

- 1. Sialidase
- 2. CMP-SA-PEG (1.2 mol eq),
 - ST3Gal3
- 3. CMP-SA (16 mol eq), ST3Gal3

a-d, i-m, r-u, z (independently selected) = 0 or 1; e-h = 1; n=0; v-y (independently selected) = 0 or 1; R = PEG.

FIG. 31K

```
NSO expressed Ifn-beta. a-d, i-m, r-u, z (independently selected) = 0 or 1; e-h = 1; n, v-y = 0; Sia (independently selected) = Sia or Gal.
```

```
    1. Sialidase and α-galactosidase
    2. α-Galactosyltransferase, UDP-Gal
    3. CMP-SA-PEG, ST3Gal3
```

```
a-d, i-m, r-u, z (independently selected) = 0 or 1;
e-h=1; R = PEG
n = 0; v-y (independently selected) = 1,
when j-m (independently selected) is 1;
```

FIG. 31L

```
CHO, BHK, 293 cells, Vero expressed Ifin-beta. a-d, i-m, r-u, z (independently selected) = 0 or 1; e-h = 1; n, v-y = 0.
```

```
1. Sialidase
2. CMP-SA-PEG (16 mol eq),
ST3Gal3
3. CMP-SA, ST3Gal3
```

```
a-d, i-m, r-u, z (independently selected) = 0 or 1; e-h = 1; n = 0; v-y (independently selected) = 0 or 1; R = PEG.
```

FIG. 31M

CHO, BHK, 293 cells, Vero expressed Ifn-beta. a-d, i-m, r-u, z (independently selected) = 0 or 1; e-h = 1; n, v-y = 0.

 CMP-SA-levulinate, ST3Gal3, buffer, salt
 H_aN₂-PEG

a-d, i-m, r-u, z (independently selected) = 0 or 1; e-h = 1; n = 0; v-y (independently selected) = 0 or 1; R = PEG.

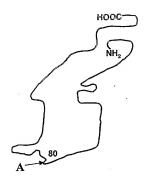
FIG. 31N

CHO, BHK, 293 cells, Vero expressed Ifin-beta. a-d, i-m, r-u, z (independently selected) = 0 or 1; e-h = 1; n, v-y = 0.

1. CMP-SA, α2,8-ST

a-d, i, r-u, z (independently selected) = 0 or 1; e-h = 1; j-m (independently selected) = 0-20; n, v-y (independently selected) = 0.

FIG. 310



$$\mathbf{A} = \begin{pmatrix} (\operatorname{Fuc})_{i} & & & & & & & & \\ \operatorname{GlcNAc-Gal})_{a}_{c}^{1} & & & & & & \\ \operatorname{GlcNAc-Gal})_{a}_{b}^{1} & & & & & \\ \operatorname{GlcNAc-Gal})_{b}_{l}^{1} & & & & & \\ \operatorname{GlcNAc-Gal})_{c}_{l}^{2} & & & & & \\ \operatorname{GlcNAc-Gal})_{d}_{h}^{2} & & & & \\ \operatorname{(GlcNAc-(Gal)_{d})_{h}^{1}} & & & & \\ \operatorname{(GlcNAc-(Gal)_{d})_{h}^{1}} & & & & \\ \operatorname{(GlcNAc-(Gal)_{d})_{h}^{1}} & & & \\ \operatorname{(GlcNAc-(Gal)_{h}^{1}} & & \\ \operatorname{(GlcNAc-(Gal)_{h}^{1}} & & & \\ \operatorname{(GlcNAc-(Gal)_$$

a-d, i, p-u (independently selected) = 0 or 1. e-h (independently selected) = 0 to 6. j-m (independently selected) = 0 to 100. v-y = 0; R = modifying group; R' = H, glycosyl group, modifying group, glycoconjugate.

FIG. 31P

Insect cell expressed Ifn-beta. a-d, f, h, j-m, s, u, v-y = 0; e, g, i, q, r, t (independently selected) = 0 or 1.

GNT's 1,2,4,5, UDP-GlcNAc
 Galactosyltransferase, UDP-Gal-PEG

a-i, q-u (independently selected) = 0 or 1; j-m=0; v-y (independently selected) = 1, when e-h (independently selected) is 1; R=PEG.

FIG. 31Q

Yeast expressed Ifn-beta. a-m = 0; q-y (independently selected) = 0 to 1; p = 1; R (branched or linear) = Man, oligomannose.

- 1. Endoglycanase
- 2. Galactosyltransferase, UDP-Gal
- 3. CMP-SA-PEG, ST3Gal3

a-m, p-y = 0; n (independently selected) = 0 or 1; R' = -Gal-Sia-PEG.

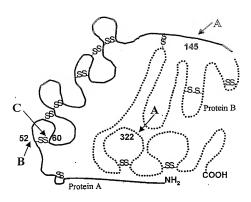
FIG. 31R

CHO, BHK, 293 cells, Vero expressed Ifn-beta. a-d, i-m, q-u (independently selected) = 0 or 1; e-h=1; v-y=0.

- 1. CMP-SA-linker-SA-CMP, ST3Gal3
- ST3Gal3, desialylated transferrin.
 CMP-SA, ST3Gal3

a-m, q-u (independently selected) = 0 or 1; p = 1; n = 0;v-y (independently selected) = 0 or 1; R = linker-transferrin.

FIG. 31S



$$\begin{array}{c} \text{(Fuc),} \\ \text{(Fuc),} \\ \text{GlcNAc-GlcNAc-Man} \\ \text{Man} & \begin{bmatrix} [\text{GlcNAc-(Gal)}_{a}]_{a}^{-} (\text{Sia})_{j}^{-} (R)_{v} \\ [\text{GlcNAc-(Gal)}_{b}]_{r}^{-} (\text{Sia})_{k}^{-} (R)_{w} \\ \end{bmatrix}_{s}^{r} \\ \text{Man} & \begin{bmatrix} [\text{GlcNAc-(Gal)}_{d}]_{a}^{-} (\text{Sia})_{r}^{-} (R)_{x} \\ [\text{GlcNAc-(Gal)}_{d}]_{b}^{-} (\text{Sia})_{m}^{-} (R)_{y} \\ \end{bmatrix}_{u}^{r} \\ \end{array}$$

$$\mathbf{B} \leftarrow \{\text{Gic-(Xyl)}_n\}_{\mathbf{0}}$$

a-d, i, q-u (independently selected) = 0 or 1. o, p (independently selected) = 0 or 1. e-h, n (independently selected) = 0 to 6. j-m (independently selected) = 0 to 20. v-y = 0; R = modifying group, mannose, oligomannose, Sia-Lewis X, Sia-Lewis A..

FIG. 32A

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```
BHK expressed Factor VII or VIIa a-d, e, i, g, q, j, l, o, p (independently selected) = 0 or 1; r, t= 1; f, h, k, m, s, u, v-y = 0; n = 0-4.
```

```
    Sialidase
    CMP-SA-PEG (16 mole eq),
    ST3Gal3
```

```
a-d, e, g, i, q, j, l, o, p (independently selected) = 0 or 1; r, t = 1; f, h, k, m, s, u, w, y = 0; n = 0-4; v, x, (independently selected) = 1, when j, 1 (respectively, independently selected) is 1; R = PEG.
```

FIG. 32B

CHO, BHK, 293 ceils, Vero expressed Factor VII or VIIa a-d, e, i, g, q, j, l, o, p (independently selected) = 0 or 1; r, t = 1; f, h, k, m, s, u, v-y = 0; n = 0-4.

```
1. Sialidase
2. CMP-SA-PEG (1.2 mole eq),
ST3Gal3
3. CMP-SA (8 mol eq), ST3Gal3
```

```
a-d, e, g, i, q, j, l, o, p (independently selected) = 0 or 1; r, t = 1; f, h, k, m, s, u, w, y = 0; n = 0-4; v or x, (independently selected) = 1, when j or l, (respectively, independently selected) is 1; R = PEG.
```

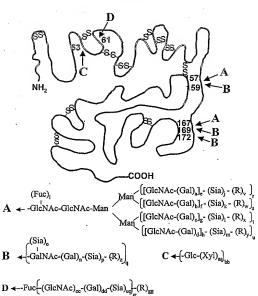
FIG. 32C

NSO expressed Factor VII or VIIa a--u (independently selected) = 0 or 1; v-y = 0; n = 0-4; Sia (independently selected) = Sia or Gal.

- Sialidase and α-galactosidase
 Galactosyltransferase, UDP-Gal
 3. CMP-SA-PEG, ST3Gal3
- a-m, o-u (independently selected) = 0 or 1; n = 0-4; v-y (independently selected) = 1, when j-m (independently selected) is 1; Sia = Sia; R = PEG.

FIG. 32D





a-d, i, n-u (independently selected) = 0 or 1.
bb, cc, dd, ee, ff, gg (independently selected) = 0 or 1.
e-h, aa (independently selected) = 0 to 6.
j-m (independently selected) = 0 to 20.
v-z = 0; R = modifying group, mannose, oligo-mannose.

FIG. 33A

```
CHO, BHK, 293 cells, Vero expressed Factor IX a-d, q=1; e-h=1 to 4; aa, bb, cc, dd, ee, ff, j-m, i, n, o, p, r-u (independently selected) = 0 or 1; v-z, gg=0.
```

Sialidase
 CMP-SA-PEG, ST3Gal3

```
a-d, q = 1; e-h = 1 to 4;
aa, bb, cc, dd, ee, ff, i, n, r-u (independently selected)
= 0 or 1;
o, p, z = 0;
j-m, ee, v-y, gg (independently selected) = 0 or 1;
R = PEG.
```

FIG. 33B

```
CHO, BHK, 293 cells, Vero expressed Factor IX a-d, n, q = 1; e-h = 1 to 4; aa, bb, cc, dd, ee, ff, j-m, i, o, p, r-u (independently selected) = 0 or 1; v-z, gg = 0.
```

- 1. Sialidase
- 2. CMP-SA-PEG, ST3Gal3 3. ST3Gal1, CMP-SA

a-d, n, p, q = 1; e-h = 1 to 4; aa, bb, cc, dd, ee, ff, i, r-u (independently selected) = 0 or 1; j-m, ee, y-y, gg (independently selected) = 0 or 1;

o, z=0; R=PEG.

FIG. 33C

CHO, BHK, 293 cells, Vero expressed Factor IX a-d, n, q, bb, cc, dd, ff = 1; e-h, aa = 1 to 4; ee, j-m, i, o, p, r-u (independently selected) = 0 or 1; v-z, gg = 0.

- 1. sialidase
- 2. Galactosyltransferase, UDP-Gal
- 3. CMP-SA, ST3Gal3 4. CMP-SA-PEG, ST3Gal1
- 4. CMP-SA-PEG, ST3Gall

```
a-d, n, q = 1; e-h = 1 to 4;
aa, bb, cc, dd, ee, ff, i, r-u (independently selected) = 0 or 1; R = PEG;
o, v-y, gg = 0;
j-m, p, ee (independently selected) = 0 or 1, but when p = 1, z = 1.
```

FIG. 33D

```
CHO, BHK, 293 cells, Vero expressed Factor IX a-d, q=1; e-h=1 to 4; aa, bb, cc, dd, ee, ff, j-m, i, n, o, p, r-u (independently selected) = 0 or 1; v-z, gg = 0.
```

CMP-SA-PEG, ST3Gal3

```
a-d, q = 1; e-h = 1 to 4;
aa, bb, cc, dd, ee, ff, i, n, r-u (independently selected) = 0 or 1; R = PEG;
o, p, z = 0; j-m, ee, v-y, gg (independently selected) = 0 or 1.
```

FIG. 33E

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```
CHO, BHK, 293 cells, Vero expressed Factor IX
a-d, q = 1; e-h = 1 to 4;
aa, bb, cc, dd, ee, ff, j-m, i, n, o, p, r-u (independently selected) = 0 or 1;
v-z, gg = 0.

1. CMP-SA-levulinate, ST3Gal3,
```

```
    CMP-SA-levulinate, ST3Gal3
buffer, salt
    H<sub>4</sub>N<sub>2</sub>-PEG
```

```
a-d, q = 1; e-h = 1 to 4;
aa, bb, cc, dd, ee, ff, i, n, r-u (independently selected)
= 0 or 1;
o, p, z = 0; R = PEG;
j-m, ee, v-y, gg (independently selected) = 0 or 1.
```

FIG. 33F

```
CHO, BHK, 293 cells, Vero expressed Factor IX a-d, n, q, bb, cc, dd, ff = 1; e-h, aa = 1 to 4; ee, j-m, i, o, p, r-u (independently selected) = 0 or 1; v-z, gg = 0.
```

```
1. CMP-SA-PEG, α2,8-ST
```

```
a-d, q = 1; e-h = 1 to 4;

aa, bb, cc, dd, ee, ff, i, n, r-u (independently selected)

= 0 or 1;

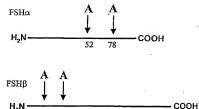
o, p, z = 0; R= PEG;

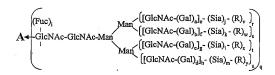
j-m, ee (independently selected) = 0 to 2;

v-y, gg (independently selected) = 1, when j-m

(independently selected) is 2;
```

FIG. 33G





a-d, i, q-u (independently selected) = 0 or 1. e-h (independently selected) = 0 to 6. j-m (independently selected) = 0 to 100. v-y = 0; R = modifying group, mannose, oligo-mannose.

FIG. 34A

CHO, BHK, 293 cells, Vero expressed FSH. a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y = 0.

```
    Sialidase
    CMP-SA-PEG (16 mol eq),
ST3Gal3
```

a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y (independently selected) = 1, when j-m (independently selected) is 1; R = PEG,

FIG. 34B

```
CHO, BHK, 293 cells, Vero expressed FSH. a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y=0.
```

```
1. Sialidase
2. CMP-SA-PEG (1.2 mol eq),
ST3Gal3
3. CMP-SA (16 mol eq), ST3Gal3
```

```
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y (independently selected) = 0 or 1;
R = PEG.
```

FIG. 34C

NSO expressed FSH.

- a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y = 0;
- Sia (independently selected) = Sia or Gal.
 - 1. Sialidase and α-galactosidase
 - 2. Galactosyltransferase, UDP-Gal
 - 3, CMP-SA-PEG, ST3Gal3

a-d, i-m, q-n (independently selected) = 0 or 1; e-h = 1; v-y (independently selected) = 1, when j-m (independently selected) is 1; R = PEG.

FIG. 34D

CHO, BHK, 293 cells, Vero expressed FSH. a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y = 0.

1. Sialidase

- 2. CMP-SA-PEG (16 mol èq), ST3Gal3
- 3. CMP-SA, ST3Gal3

a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y (independently selected) = 0 or 1; R = PEG.

FIG. 34E

```
CHO, BHK, 293 cells, Vero expressed FSH. a-d, i-m, q-u (independently selected) = 0 or 1; e-h=1; v-y=0.
```

```
    CMP-SA-levulinate, ST3Gal3,
buffer, salt
    H<sub>a</sub>N<sub>7</sub>-PEG
```

a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y (independently selected) = 0 or 1; R = PEG.

FIG. 34F

CHO, BHK, 293 cells, Vero expressed FSH. a-d, i-m, q-u (independently selected) = 0 or 1; e-h=1; v-y=0.

1. CMP-SA, α2,8-ST

a-d, i, q-u (independently selected) = 0 or 1; e-h = 1; j-m (independently selected) = 0-20; v-y (independently selected) = 0.

· FIG. 34G

```
Insect cell expressed FSH.
a-d, f, h, j-m, s, u, v-y = 0;
e, g, i, q, r, t (independently selected) = 0 or 1.
```

GNT's 1,2,4,5, UDP-GlcNAc
 Galactosyltransferase, UDP-Gal-PEG

```
a-i, q-u (independently selected) = 0 or 1;
j-m=0; v-y (independently selected) = 1,
when e-h (independently selected) is 1;
R = PEG.
```

FIG. 34H

```
Yeast expressed FSH.

a-m=0; q-y (independently selected) = 0 to 1;

p=1;

R (branched or linear) = Man, oligomannose.
```

- Endoglycanase
 Galactosyltransferase, UDP-Gal
- ★ 3. CMP-SA-PEG, ST3Gal3

```
a-m, p-y = 0;
n (independently selected) = 0 or 1;
R' = -Gal-Sia-PEG.
```

FIG. 341

CHO, BHK, 293 cells, Vero expressed FSH. a-d, i-m, q-u (independently selected) = 0 or 1; e-h=1; v-y=0.

CMP-SA-linker-SA-CMP, ST3Gal3
 ST3Gal1, desialylated chorionic gonadrophin (CG) produced in CHO.
 CMP-SA, ST3Gal3, ST3Gal1

a-m, q-u (independently selected) = 0 or 1; p = 1; n = 0; v-y (independently selected) = 0 or 1; R = linker-CG.

FIG. 34J

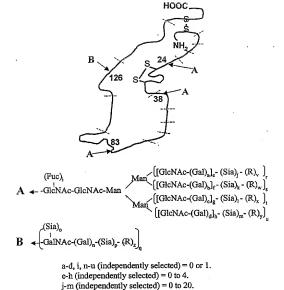


FIG. 35A

v-z = 0; R = polymer.

CHO, BHK, 293 cells, Vero expressed EPO a-g, n, q = 1; h=1 to 3; j-m, i, o, p (independently selected) = 0 or 1; r-u (independently selected) = 0 to 1; v-z = 0

Sialidase
 CMP-SA-PEG, ST3Gal3

```
a-g, n, q = 1; h = 1 to 3;
i, o, p (independently selected) = 0 or 1;
r-u (independently selected) = 0 or 1;
j-m, v-y (independently selected) = 0 or 1;
R = PEG; z = 0.
```

FIG. 35B

```
Insect cell expressed EPO a-d, f, h, j-q, s, u, v-z = 0; e, g, i, r, t (independently selected) = 0 or 1.
```

- GNT's 1&2, UDP-GlcNAc
 Galactosyltransferase, UDP-Gal
- ↓ 2. CMP-SA-PEG, ST3Gal3

 $\begin{array}{l} b,\,d,\,f,\,h,\,k,\,m\text{-}q,\,s,\,u,\,w,\,y,\,z=0;\\ a,\,c,\,e,\,g,\,i,\,r,\,t\ \mbox{(independently selected)=0 or 1;}\\ j,\,l,\,v,\,x\,\mbox{(independently selected)=0 or 1;}\\ R=PEG. \end{array}$

FIG. 35C

```
CHO, BHK, 293 cells, Vero expressed EPO a-q, r-u (independently selected) = 0 or 1; v-z=0.
```

- 1. sialidase
- 2. Galactosyltransferase, UDP-Gal
- 3. CMP-SA, ST3Gal3
- 4. CMP-SA-PEG, ST3Gall

 4. CMP-SA-PEG, ST3Gall

 4. CMP-SA-PEG, ST3Gall

 4. CMP-SA-PEG, ST3Gall

 4. CMP-SA-PEG, ST3Gall

```
a-h, n, q = 1;
i-m, o, r-u (independently selected) = 0 or 1;
v-y = 0; p, z = 0 or 1; R = PEG.
```

FIG. 35D

```
CHO, BHK, 293 cells, Vero expressed EPO a-g, n, q = 1; h = 1 to 3; j-m, i, o, p (independently selected) = 0 or 1; r-u (independently selected) = 0 or 1; v-z = 0
```

```
1. CMP-SA-PEG, ST3Gal3
```

```
a-g, n, q = 1; h = 1 to 3;
i, o, p (independently selected) = 0 or 1;
r-u (independently selected) = 0 to 1;
j-m, v-y (independently selected) = 0 or 1;
R = PEG; z = 0.
```

FIG. 35E

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Insect cell, yeast or fungi expressed EPO a-d, f, h, j-q, s, u, v-z = 0; e, g, i, r, t (independently selected) = 0 or 1.

```
1. GNT's 1, 2 & 5, UDP-GIcNAc
2. Galactosyltransferase, UDP-Gal-PEG
```

```
    a-c, e-g, i, r-t, v-x (independently selected) =
    0 or 1;
    d, h, j-q, u, y, z = 0;
    R = PEG.
```

FIG. 35F

Insect cell, yeast or fungi expressed EPO a-d, f, h, j-q, s, u, v-z = 0; e, g, i, r, t (independently selected) = 0 or 1.

 GNT's 1, 2 & 5, UDP-GlcNAc
 Galactosidase (synthetic enzyme), PEG-Gal-F.

a-c, e-g, n, q-t, v-x, z (independently selected) = 0 or 1; d, h, j-m, o, p, y, z = 0; R = PEG.

FIG. 35G

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Insect cell, yeast or fungi expressed EPO a-d, f, h, j-m, n-q, s, u, v-z = 0; e, g, i, r, t (independently selected) = 0 or 1.

1. GNT-1, UDP-GIcNAc-PEG

e, i, r, v (independently selected) = 0 or 1; a-h, j-q, s-u, w-z = 0; R = PEG.

FIG. 35H

Insect cell, yeast or fungi expressed EPO a-d, f, h, j-m, n-q, s, u, v-z = 0; e, g, i, r, t (independently selected) = 0 or 1.

GNT-1, UDP-GlcNAc
 Galactosyltransferase, UDP-Gal-PEG

a, e, i, r, v (independently selected) = 0 or 1; b-d, f-h, j-q, s-u, w-z = 0; R = PEG.

FIG. 351

Insect cell, yeast or fungi expressed EPO a-d, f, h, j-m, n-q, s, u, v-z = 0; e, g, i, r, t (independently selected) = 0 or 1.

- 1. GNT-1, UDP-GlcNAc
- 2. Galactosyltransferase, UDP-Gal
- → 3. ST3Gal3, CMP-SA-PEG

a, e, i, j, r, v (independently selected) = 0 or 1; b-d, f-h, k-q, s-u, w-z = 0; R = PEG.

FIG. 35J

Insect cell, yeast or fungi expressed EPO a-d, f, h, j-m, n-q, s, u, v-z = 0; e, g, i, r, t (independently selected) = 0 or 1.

- 1, GNT's 1, 2 & 5, UDP-GlcNAc
- 2. Galactosyltransferase, UDP-Gal
- 3. ST3Gal3, CMP-SA-PEG

a-c, e-g, i-l, r-t, v-x (independently selected) = 0 or 1;

d, h, m-q, u, y, z = 0; R = PEG.

FIG. 35K

Insect cell, yeast or fungi expressed EPO a-d, f, h, j-m, n-q, s, u, v-z = 0; e, g, i, r, t (independently selected) = 0 or 1.

- 1. GNT's 1, 2 & 5, UDP-GlcNAc
- 2. Galactosyltransferase, UDP-Gal
- ▼ 3. α2,6-sialyltransferase, CMP-SA-PEG

```
a-c, e-g, i-l, r-t, v-x (independently selected)
= 0 or 1;
d, h, m-q, u, y, z = 0; R = PEG.
```

FIG. 35L

CHO, BHK, 293 cells, Vero expressed EPO a-q, r-u (independently selected) = 0 or 1; v-z = 0.

- sialidase
 CMP-SA, ST3Gal3
- 3. CMP-SA-PEG, ST3Gal1

a-h, q, i-o, r-u (independently selected) = 0 or 1; v-y = 0; p, z = 0 or 1; R = PEG.

FIG. 35M

CHO, BHK, 293 cells, Vero expressed EPO a-q, r-u (independently selected) = 0 or 1; v-z=0.

CMP-SA-PEG, ST3Gal3

a-h, i-o, q-u (independently selected) = 0 or 1; v-y = 0; p, z = 0 or 1; R = PEG.

FIG. 35N

CHO, BHK, 293 cells, Vero expressed EPO a-q, r-u (independently selected) = 0 or 1; y-z = 0.

1, CMP-SA-PEG, α 2,8-sialyltransferase

a-h, i-o, q-u (independently selected) = 0 or 1; v-y = 0; p, z = 0 or 1; R = SA-PEG.

FIG. 350

CHO, BHK, 293 cells, Vero expressed EPO
a-q, r-u (independently selected) = 0 or 1;
v-z = 0.

1. CMP-SA-PEG, α2,8-sialyltransferase
a-h, i-o, p-u, v-z (independently selected)
= 0 or 1;
R = SA-PEG.

FIG. 35P

yeast or fungi expressed EPO r, t, u, v, x, y (independently selected) = 0 or 1; a-m, n-q, s, w, z = 0; $R = (Man)_n$ where n = 1-5, linear or branched.

mannosidases
 GNT-1, UDP-GlcNAc
 galactosyltransferase, UDP-Gal
 ST3Gal3, CMP-SA-PEG

a, e, j, r, v (independently selected) = 0 or 1; b-d, f-i, k-q, s-u, w-z = 0; R = PEG.

FIG. 35Q

yeast or fungi expressed EPO
r, t, u, v, x, y (independently selected) = 0 or 1;
a-m, n-q, s, w, z = 0; R = (Man)_n
where n = 1-5, linear or branched.

mannosidases
 GNT-1, UDP-GlcNAc-PEG

e, r, v (independently selected) = 0 or 1; a-h, i-q, s-u, w-z = 0; R = PEG.

FIG. 35R

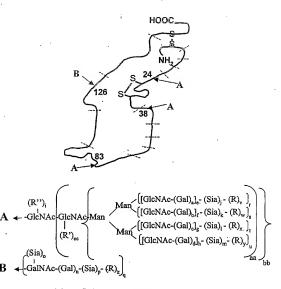
yeast or fungi expressed EPO r, t, u, v, x, y (independently selected) = 0 or 1; a-m, n-q, s, w, z = 0; $R = (Man)_n$ where n = 1-5, linear or branched.

- 1. mannosidase-I
 2. GNT-1, UDP-GlcNAc
 3. galactosyltransferase, UDP-Gal
 4. ST3Gal3, CMP-SA-PEG
- a, e, j, r, t-u, v, x, y (independently selected) = 0 or 1; b-d, f-i, k-q, s, w, z = 0; (R)_v = PEG; (R)_x and (R)_v = Man.

FIG. 35S

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a-d, i, n-u (independently selected) = 0 or 1. e-h (independently selected) = 0 to 4. j-m (independently selected) = 0 to 20. v-z=0; aa, bb=1; cc=0; R=polymer; R" and R'= sugar-polymer or Fuc.

FIG. 35T

```
yeast or fungi expressed EPO

r, t, u, v, x, y (independently selected) = 0 or 1;

cc, a-m, n-q, s, w, z = 0;

aa, bb = 1;

R = (Man), where n = 1-100, linear or branched.

1. endo-H

2. galactosyltransferase, UDP-Gal-PEG

i (independently selected) = 0 or 1;
```

aa, bb, cc, a-h, j-z = 0; R'' = Gal-PEG.

FIG. 35U

```
yeast or fungi expressed EPO
r, t, u, v, x, y (independently selected) = 0 or 1;
cc, a-m, n-q, s, w, z = 0; aa, bb = 1;
R = (Man), where n = 1-100, linear or branched.

1. endo-H
2. galactosyltransferase, UDP-Gal
3. ST3Gal3, CMP-SA-PEG

i (independently selected) = 0 or 1;
aa, bb, cc, a-h, j-z = 0; R" = Gal-SA-PEG.
```

FIG. 35V

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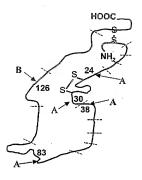
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Insect cell expressed EPO a-d, f, h, j-m, n-q, s, u, v-z=0; e, g, i, r, t (independently selected) = 0 or 1; aa = 1; R"=Fuc.

- 1. mannosidases
- 2. galactosyltransferase, UDP-Gal-PEG

cc, e, i, r, v (independently selected) = 0 or 1; bb, a-h, j-q, s-u, w-z = 0; aa = 1; R' = Gal-PEG:

FIG. 35W



$$(Fuc)_{i} \\ A \leftarrow -GlcNAc-GlcNAc-Man \\ \left[[GlcNAc-(Gal)_{a}]_{a}^{*} \cdot (Sia)_{j} \cdot (R)_{v} \right]_{i} \\ Man \\ \left[[GlcNAc-(Gal)_{h}]_{r} \cdot (Sia)_{k}^{*} - (R)_{w} \right]_{s} \\ Man \\ \left[[GlcNAc-(Gal)_{a}]_{g}^{*} \cdot (Sia)_{h}^{*} \cdot (R)_{w} \right]_{t} \\ \left[[GlcNAc-(Gal)_{d}]_{h}^{*} \cdot (Sia)_{m}^{*} \cdot (R)_{y} \right]_{u} \\ B \leftarrow \left[GlcNAc-(Gal)_{a}^{*} \cdot (Sia)_{p}^{*} \cdot (R)_{z} \right]_{q} \\ a-d, i, n-u (independently selected) = 0 \text{ or } 1.$$

a-d, i, n-u (independently selected) = 0 or 1. e-li (independently selected) = 0 to 4. j-m (independently selected) = 0 to 20. v-z = 0; R = polymer.

FIG. 35X

```
\label{eq:NSO} \begin{array}{l} NSO \; expressed \; NESP \\ q = 1; \; a\text{-i}, \, n, \, r\text{-u} \; (independently \; selected) = 0 \\ or \; 1; \; j\text{-m}, \, o, \, p, \, v\text{-}z = 0 \end{array}
```

```
    CMP-SA-levulinate, ST3Gal3,
buffer, salt
    H<sub>4</sub>N<sub>2</sub>-PEG
```

```
q = 1; a-i, j-n, r-y (independently selected) = 0 or 1; 
o, p, z = 0; R = PEG.
```

FIG. 35Y

```
CHO, BHK, 293 cells, Vero expressed NESP a-g, n, q = 1; h = 1 to 3; j-m, i, o, p (independently selected) = 0 or 1; r-u (independently selected) = 0 or 1; v-z = 0
```

1. CMP-SA-PEG, α 2,8-ST

```
a-g, n, q = 1; h = 1 to 3;
i, o, p (independently selected) = 0 or 1;
r-u (independently selected) = 0 to 1;
j-m (independently selected) = 0 to 2;
v-y (independently selected) = 1,
when j-m (independently selected) is 2;
R = PEG; z = 0.
```

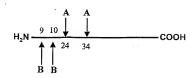
FIG. 35Z

CHO, BHK, 293 cells, Vero expressed NESP a-g, n, q = 1; h = 1 to 3; j-m, i, o, p (independently selected) = 0 or 1; r-u (independently selected) = 0 to1; v-z= 0

1 CMP-SA, poly-α2,8-ST

a-g, n, q = 1; h=1 to 3; i, j-m, o, p, r-u, (independently selected) = 0 or 1; v-z (independently selected) = 0-40; R = Sia.

FIG. 35AA



$$\mathbf{A} \leftarrow \begin{bmatrix} (\operatorname{Fuc})_i & & & \\ (\operatorname{Fuc})_i & & & \\ (\operatorname{GlcNAc-GlcNAc-Man} & & & \\ (\operatorname{GlcNAc-GlcNAc-Man} & & & \\ (\operatorname{GlcNAc-Gal})_b]_r \cdot (\operatorname{Sia})_j \cdot (R)_v \end{bmatrix}_r \\ \mathbf{Man} \begin{bmatrix} (\operatorname{GlcNAc-(Gal)}_a]_g - (\operatorname{Sia})_j \cdot (R)_y \end{bmatrix}_r \\ (\operatorname{IGlcNAc-(Gal)}_d]_h \cdot (\operatorname{Sia})_m - (R)_y \end{bmatrix}_u \\ \mathbf{Man} \begin{bmatrix} (\operatorname{GlcNAc-(Gal)}_d)_h \cdot (\operatorname{Sia})_m - (R)_y \end{bmatrix}_u \\ \mathbf{Man} \begin{bmatrix} (\operatorname{GlcNAc-(Gal)}_d)_h \cdot (\operatorname{Sia})_m - (R)_y \end{bmatrix}_u \\ \mathbf{Man} \begin{bmatrix} (\operatorname{GlcNAc-(Gal)}_d)_h \cdot (\operatorname{Sia})_m - (R)_y \end{bmatrix}_u \\ \mathbf{Man} \begin{bmatrix} (\operatorname{GlcNAc-(Gal)}_d)_h \cdot (\operatorname{Sia})_m - (R)_y \end{bmatrix}_u \\ \mathbf{Man} \begin{bmatrix} (\operatorname{GlcNAc-(Gal)}_d)_h \cdot (\operatorname{Sia})_m - (R)_y \end{bmatrix}_u \\ \mathbf{Man} \begin{bmatrix} (\operatorname{GlcNAc-(Gal)}_d)_h \cdot (\operatorname{Sia})_m - (R)_y \end{bmatrix}_u \\ \mathbf{Man} \begin{bmatrix} (\operatorname{GlcNAc-(Gal)}_d)_h \cdot (\operatorname{Sia})_m - (R)_y \end{bmatrix}_u \\ \mathbf{Man} \begin{bmatrix} (\operatorname{GlcNAc-(Gal)}_d)_h \cdot (\operatorname{Sia})_m - (R)_y \end{bmatrix}_u \\ \mathbf{Man} \begin{bmatrix} (\operatorname{GlcNAc-(Gal)}_d)_h \cdot (\operatorname{Sia})_m - (R)_y \end{bmatrix}_u \\ \mathbf{Man} \begin{bmatrix} (\operatorname{GlcNAc-(Gal)}_d)_h \cdot (\operatorname{Sia})_m - (R)_y \end{bmatrix}_u \\ \mathbf{Man} \begin{bmatrix} (\operatorname{GlcNAc-(Gal)}_d)_h \cdot (\operatorname{Sia})_m - (R)_y \end{bmatrix}_u \\ \mathbf{Man} \begin{bmatrix} (\operatorname{GlcNAc-(Gal)}_d)_h \cdot (\operatorname{Sia})_m - (R)_y \end{bmatrix}_u \\ \mathbf{Man} \begin{bmatrix} (\operatorname{GlcNAc-(Gal)}_d)_h \cdot (\operatorname{Sia})_m - (R)_y \end{bmatrix}_u \\ \mathbf{Man} \begin{bmatrix} (\operatorname{GlcNAc-(Gal)}_d)_h \cdot (\operatorname{Sia})_m - (R)_y \end{bmatrix}_u \\ \mathbf{Man} \begin{bmatrix} (\operatorname{GlcNAc-(Gal)}_d)_h \cdot (\operatorname{Sia})_m - (R)_y \end{bmatrix}_u \\ \mathbf{Man} \begin{bmatrix} (\operatorname{GlcNAc-(Gal)}_d)_h \cdot (\operatorname{Sia})_m - (R)_y \end{bmatrix}_u \\ \mathbf{Man} \begin{bmatrix} (\operatorname{GlcNAc-(Gal)}_d)_h \cdot (\operatorname{Sia})_m - (R)_y \end{bmatrix}_u \\ \mathbf{Man} \begin{bmatrix} (\operatorname{GlcNAc-(Gal)}_d)_h \cdot (\operatorname{Gal}_d)_h \cdot (\operatorname{Gal}_d)_h \cdot (\operatorname{Gal}_d)_h \\ \mathbf{Man} \begin{bmatrix} (\operatorname{GlcNAc-(Gal)}_d)_h \cdot (\operatorname{Gal}_d)_h \cdot (\operatorname{Gal}_d)_h \\ \mathbf{Man} \begin{bmatrix} (\operatorname{GlcNAc-(Gal)}_d)_h \cdot (\operatorname{Gal}_d)_h \cdot (\operatorname{Gal}_d)_h \\ \mathbf{Man} \begin{bmatrix} (\operatorname{GlcNAc-(Gal)}_d)_h \cdot (\operatorname{Gal}_d)_h \cdot (\operatorname{Gal}_d)_h \\ \mathbf{Man} \begin{bmatrix} (\operatorname{Gal}_d)_h \cdot (\operatorname{Gal}_d)_h \cdot (\operatorname{Gal}_d)_h \\ \mathbf{Man} \end{bmatrix}_u \\ \mathbf{Man} \begin{bmatrix} (\operatorname{Gal}_d)_h \cdot (\operatorname{Gal}_d)_h \cdot (\operatorname{Gal}_d)_h \cdot (\operatorname{Gal}_d)_h \\ \mathbf{Man} \begin{bmatrix} (\operatorname{Gal}_d)_h \cdot (\operatorname{Gal}_d)_h \cdot (\operatorname{Gal}_d)_h \\ \mathbf{Man} \end{bmatrix}_u \\ \mathbf{Man} \begin{bmatrix} (\operatorname{Gal}_d)_h \cdot (\operatorname{Gal}_d)_h \cdot (\operatorname{Gal}_d)_h \cdot (\operatorname{Gal}_d)_h \\ \mathbf{Man} \end{bmatrix}_u \\ \mathbf{Man} \begin{bmatrix} (\operatorname{Gal}_d)_h \cdot (\operatorname{Gal}_d)_h \cdot (\operatorname{Gal}_d)_h \cdot (\operatorname{Gal}_d)_h \\ \mathbf{Man} \end{bmatrix}_u \\ \mathbf{Man} \begin{bmatrix} (\operatorname{Gal}_d)_h \cdot (\operatorname{Gal}_d)_h \cdot (\operatorname{Gal}_d)_h \\ \mathbf{Man} \end{bmatrix}_u \\ \mathbf{Man} \begin{bmatrix} (\operatorname{Gal}_d)_h \cdot (\operatorname{Gal}_d)_h \cdot (\operatorname{Gal}_d)_h \\ \mathbf{Man} \end{bmatrix}_u \\ \mathbf{Man} \begin{bmatrix} (\operatorname{Gal}_d)_h \cdot (\operatorname{$$

$$\mathbf{B} \leftarrow \begin{pmatrix} (\operatorname{Sia})_{o} \\ -(\operatorname{GalNAc-(Gal)}_{n} - (\operatorname{Sia})_{p} - (R)_{z} \end{pmatrix}_{aa}$$

a-d, i, n-u, aa (independently selected) = 0 or 1. e-h (independently selected) = 0 to 6. j-m (independently selected) = 0 to 100. v-y = 0; R = polymer, glycoconjugate.

FIG. 36A

```
CHO, BHK, 293 cells, Vero expressed GM-CSF.
a-d, i-m, o-u, aa (independently selected) = 0 or 1;
n, e-h = 1; v-z = 0.

1. Sialidase
2. CMP-SA-PEG (16 mol eq),
ST3Gal3
```

```
a-d, i-m, q-u, aa (independently selected) = 0 or 1;
o, p, z = 0; n, e-h = 1;
v-y (independently selected) = 1,
when j-m (independently selected) is 1;
R = PEG.
```

FIG. 36B

```
CHO, BHK, 293 cells, Vero expressed GM-CSF. a-d, i-m, o-u, aa (independently selected) = 0 or 1; n, e-h = 1; v-z = 0.
```

```
1. Sialidase
2. CMP-SA-PEG (1.2 mol eq),
$T3Gal3

▼ 3. CMP-SA (16 mol eq), $T3Gal3 &
$T3Gal1
```

```
\begin{array}{lll} a\text{-d}, i\text{-m}, p\text{-u}, aa \text{ (independently selected)} = 0 \text{ or } 1;\\ o, z=0; & n, e\text{-h}=1;\\ v\text{-y (independently selected)} = 0 \text{ or } 1; & R=PEG. \end{array}
```

FIG. 36C

```
NSO expressed GM-CSF.
a-d, i-m, o-u, aa (independently selected) = 0 or 1;
n, e-h = 1; v-z = 0;
Sia (independently selected) = Sia or Gal.
```

- Sialidase and α-galactosidase
 CMP-SA, ST3Gal3
- CMP-SA-PEG, ST3Gal1

a-d, i-m, p-u, z, as (independently selected) = 0 or 1; n, e-h = 1; o, v-y = 0; z = 1, when p = 1; R = PEG.

FIG. 36D

```
CHO, BHK, 293 cells, Vero expressed GM-CSF. a-d, i-m, o-u, aa (independently selected) = 0 or 1; n, e-h = 1; v-z = 0.
```

- Sialidase
- CMP-SA-PEG (16 mol eq), ST3Gal3
- 3. CMP-SA, ST3Gal3

a-d, i-m, q-y, as (independently selected) = 0 or 1; o, p, z = 0; n, e-h = 1; R = PEG.

FIG. 36E

CHO, BHK, 293 cells, Vero expressed GM-CSF. a-d, i-m, o-u, aa (independently selected) = 0 or 1; n, e-h = 1; v-z=0.

 CMP-SA-levulinate, ST3Gal3, buffer, salt
 H₂N₂-PEG

a-d, i-m, o-y, aa (independently selected) = 0 or 1; z = 0; n, e-h = 1; R = PEG.

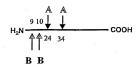
FIG. 36F

CHO, BHK, 293 cells, Vero expressed GMCSF. a-d, i-m, o-u, aa (independently selected) = 0 or 1; n, e-h = 1; v-z = 0.

1. CMP-SA, α2,8-ST

a-d, i, o-u, aa (independently selected) = 0 or 1; n, e-h = 1; j-m (independently selected) = 0-20; v-z (independently selected) = 0.

FIG. 36G



$$A \leftarrow \begin{bmatrix} (\operatorname{Fuc})_{i} \\ \operatorname{GlcNAc-Gal})_{a}_{b}^{-} \cdot (\operatorname{Sia})_{j}^{-} \cdot (\operatorname{Rio})_{j} \\ \operatorname{GlcNAc-Gal})_{b}_{l}^{-} \cdot (\operatorname{Sia})_{k}^{-} \cdot (\operatorname{Rio})_{k}^{-} \\ \operatorname{GlcNAc-Gal})_{b}_{l}^{-} \cdot (\operatorname{Sia})_{k}^{-} \cdot (\operatorname{Rio})_{k}^{-} \\ \operatorname{GlcNAc-Gal})_{b}_{l}^{-} \cdot (\operatorname{Sia})_{l}^{-} \cdot (\operatorname{Rio})_{l}^{-} \\ \operatorname{GlcNAc-Gal})_{d}_{l}^{-} \cdot (\operatorname{Sia})_{m}^{-} \cdot (\operatorname{Rio})_{l}^{-} \\ \operatorname{GlcNAc-Gal})_{d}_{l}^{-} \cdot (\operatorname{Sia})_{m}^{-} \cdot (\operatorname{Rio})_{l}^{-} \\ \operatorname{GlcNAc-Gal})_{d}_{l}^{-} \cdot (\operatorname{Sia})_{l}^{-} \cdot (\operatorname{Rio})_{l}^{-} \\ \operatorname{GlcNAc-Gal})_{d}_{l}^{-} \cdot (\operatorname{Sia})_{l}^{-} \cdot (\operatorname{Rio})_{l}^{-} \\ \operatorname{GlcNAc-Gal})_{d}^{-} \cdot (\operatorname{Sia})_{l}^{-} \cdot (\operatorname{Rio})_{l}^{-} \cdot (\operatorname{Rio})_{l}^{-} \cdot (\operatorname{Rio})_{l}^{-} \\ \operatorname{GlcNAc-Gal})_{d}^{-} \cdot (\operatorname{Rio})_{l}^{-} \cdot (\operatorname{Rio})_{l}^{-}$$

$$\mathbf{B} \leftarrow \begin{bmatrix} (\operatorname{Sia})_{0} \\ -(\operatorname{GalNAc-(Gal)}_{n} - (\operatorname{Sia})_{p} - (R)_{z} \end{bmatrix}_{n}$$

a-d, i, n-u, aa, bb, cc (independently selected) = 0 or 1.
e-h (independently selected) = 0 to 6.
j-m (independently selected) = 0 to 100.
v-y = 0; R = modifying group, mannose, oligo-mannose.
R'=H, glycosyl residue, modifying group. glycoconjugate.

FIG. 36H

```
Insect cell expressed GM-CSF.
a-d, f, h, j-m, o, p, s, u, v-z = 0;
e, g, i, n, q, r, t, aa (independently selected) = 0 or 1.
```

```
1. GNT's 1,2,4,5, UDP-GlcNAc, 2. Galactosyltransferase, UDP-Gal-PEG
```

```
a-i, n, q-u (independently selected) = 0 or 1;
j-m = 0; v-y (independently selected) = 1,
when e-h (independently selected) is 1;
R = PEG.
```

FIG. 361

```
Yeast expressed GM-CSF.
a-p, z, cc = 0;
q-y, aa (independently selected) = 0 to 1;
bb = 1; R (branched or linear) = Man, oligomamnose;
GalNAc = Man.
```

```
    Endoglycanase
    mannosidase (if aa = 1).
```

3. Galactosyltransferase, UDP-Gal-PEG

```
a-p, r-z, aa, bb = 0;
q, cc (independently selected) = 0 or 1;
R' = -Gal-PEG.
```

FIG. 36J

CHO, BHK, 293 cells, Vero expressed GM-CSF. a-m, o-u, aa, bb (independently selected) = 0 or 1; n, v-z, cc = 0.

- 1. sialidase
- 2. CMP-SA, ST3Gal3
 2. CMP-SA-linker-SA-CMP, ST3Gal1
 3. ST3Gal3, transferrin

a--m, p-u, z, aa (independently selected) = 0 or 1; o, v-y, cc = 0; bb, n = 1; R = transferrin.

FIG. 36K



$$\mathbf{A} \leftarrow \begin{bmatrix} [GlcNAc-(Gal)_{a}]_{a}^{*} \cdot (Sia)_{j}^{-} \cdot (R)_{v} \\ [GlcNAc-GicNAc-Man] \end{bmatrix}_{man} \begin{bmatrix} [GlcNAc-(Gal)_{a}]_{a}^{*} \cdot (Sia)_{j}^{-} \cdot (R)_{v} \\ [[GlcNAc-(Gal)_{b}]_{j}^{-} \cdot (Sia)_{k}^{-} \cdot (R)_{v} \\ [[GlcNAc-(Gal)_{a}]_{a}^{*} \cdot (Sia)_{m}^{-} \cdot (R)_{y} \end{bmatrix}_{u} \end{bmatrix}_{u}$$

a-d, i, q-u (independently selected) = 0 or 1. e-h (independently selected) = 0 to 6. j-m (independently selected) = 0 to 100. v-y = 0; R = polymer.

FIG. 37A

```
CHO, BHK, 293 cells, Vero expressed IF-gamma. a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y = 0.
```

```
1. Sialidase
2. CMP-SA-PEG (16 mol eq), .
```

```
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y (independently selected) = 1,
when j-m (independently selected) is 1;
R = PEG.
```

FIG. 37B

```
CHO, BHK, 293 cells, Vero expressed IF-gamma.
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y = 0.
```

```
    Sialidase
    CMP-SA-PEG (1.2 mol eq),
    ST3Gal3
    CMP-SA (16 mol eq), ST3Gal3
```

```
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y (independently selected) = 0 or 1;
R = PEG.
```

FIG. 37C

WO 2004/099231 PCT/US2004/011494

133/497

```
NSO expressed Interferon gamma.
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y = 0;
Sia (independently selected) = Sia or Gal.
```

```
    Sialidase and α-galactosidase
    α-Galactosyltransferase, UDP-Gal
    CMP-SA-PEG, ST3Gal3
```

```
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y (independently selected) = 1,
when j-m (independently selected) is 1;
R = PEG.
```

FIG. 37D

```
CHO, BHK, 293 cells, Vero expressed
Interferon gamma.
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y = 0.

1. Sialidase
```

```
    Sialidase
    CMP-SA-PEG (16 mol eq),
ST3Gal3
    CMP-SA, ST3Gal3
```

```
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y (independently selected) = 0 or 1;
R = PEG.
```

FIG. 37E

```
CHO, BHK, 293 cells, Vero expressed
Interferon gamma.
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y = 0.

1. CMP-SA-levulinate, ST3Gal3,
2. H,N,-PEG
```

```
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y (independently selected) = 0 or 1;
R = PEG.
```

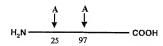
FIG. 37F

```
CHO, BHK, 293 cells, Vero expressed
Interferon gamma.
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y = 0.

1. CMP-SA, \(\alpha\).8-ST
```

```
a-d, i, q-u (independently selected) = 0 or 1;
e-h = 1; j-m (independently selected) = 0-20;
v-y (independently selected) = 0.
```

FIG. 37G



$$\mathbf{A} \leftarrow \begin{bmatrix} (\operatorname{Fuc})_{i} \\ \operatorname{GlcNAc-Gal})_{a} \end{bmatrix}_{e} - (\operatorname{Sia})_{i} - (\operatorname{R})_{v} \end{bmatrix} \\ \begin{bmatrix} (\operatorname{GlcNAc-Gal})_{b} \end{bmatrix}_{f} - (\operatorname{Sia})_{f} - (\operatorname{R})_{w} \end{bmatrix}_{e} \\ \begin{bmatrix} (\operatorname{GlcNAc-Gal})_{b} \end{bmatrix}_{f} - (\operatorname{Sia})_{f} - (\operatorname{R})_{w} \end{bmatrix}_{f} \\ (\operatorname{R}')_{n} \\ \end{bmatrix} \\ \mathbf{Man} \begin{bmatrix} (\operatorname{GlcNAc-Gal})_{d} \end{bmatrix}_{h} - (\operatorname{Sia})_{n} - (\operatorname{R})_{y} \end{bmatrix}_{u} \\ \mathbf{q}_{p} \end{bmatrix}$$

a-d, i, n, p-u (independently selected) = 0 or 1. e-h (independently selected) = 0 to 6. j-m (independently selected) = 0 to 100. v-y = 0; R = modifying group, mannose, oligo-mannose; R* = H, glycosyl residue, modifying group, glycoconjugate.

FIG. 37H

```
Insect or fungi cell expressed IF-gamma. a-d, f, h, j-m, s, u, v-y = 0; c, g, i, q, r, t (independently selected) = 0 or 1.
```

```
    GNT's 1,2,4,5, UDP-GlcNAc
    Galactosyltransferase, UDP-Gal-PEG
```

```
a-i, q-u (independently selected) = 0 or 1;
j-m = 0; v-y (independently selected) = 1,
when e-h (independently selected) is 1;
R = PEG.
```

FIG. 371

```
Yeast expressed IF-gamma. a-m=0; q-y (independently selected) = 0 to 1; p=1; R (branched or linear) = Man, oligomannose.
```

- Endoglycanase
- 2. Galactosyltransferase, UDP-Gal
- 3. CMP-SA-PEG, ST3Gal3

```
a-m, p-y = 0; n (independently selected) = 0 or 1;
R' = -Gal-Sia-PEG.
```

FIG. 37J

```
CHO, BHK, 293 cells, Vero expressed IF-gamma. a-d, i-m, q-u (independently selected) = 0 or 1; e-h=1; v-y=0.
```

- 1. CMP-SA-linker-Gal-UDP, ST3Gal3
- Galactosyltransferase, transferrin treated with endoglycanase.

```
a-m, q-u (independently selected) = 0 or 1;
p = 1; n = 0;
v-y (independently selected) = 0 or 1;
R = linker-transferrin.
```

FIG. 37K

```
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h, p = 1; n, v-y = 0.

1. CMP-SA-PEG,
ST3Gal3

a-d, i-m, q-u (independently selected) = 0 or 1;
e-h, p = 1;
n, v-y (independently selected) = 0 or 1;
```

CHO, BHK, 293 cells, Vero expressed

Interferon gamma.

FIG. 37L

R = PEG.

```
Insect or fungi cell expressed IF-gamma.
a-d, f, h, j-n, s, u, v-y = 0;
e, g, i, q, r, t (independently selected) = 0 or 1.

1. GNT's 1 & 2, UDP-GlcNAc-PEG

a-d, f, h, j-n, s, u, w, y = 0;
e, g, i, r, t, q (independently selected) = 0 or 1;
p = 1; v, x (independently selected) = 1,
when e, g (independently selected) is 1;
R = PEG.
```

FIG. 37M

```
Interferon gamma.

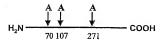
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y = 0.

1. CMP-SA-PEG, \(\alpha 2.8\)-ST

a-d, i, q-u (independently selected) = 0 or 1;
e-h = 1; j-m (independently selected) = 0-2;
v-y (independently selected) = 1,
when j-m (independently selected) = 2;
R = PEG.
```

CHO, BHK, 293 cells, Vero expressed

FIG. 37N



$$\mathbf{A} = \underbrace{\left\{ \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{a} \end{bmatrix}_{c}^{c} \left(\operatorname{Sia} \right)_{j}^{-} \left(\operatorname{R} \right)_{v} \\ \left\{ \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{a} \end{bmatrix}_{c}^{-} \left(\operatorname{Sia} \right)_{j}^{-} \left(\operatorname{R} \right)_{v} \\ \right\}_{s}^{c} \\ \left\{ \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{a} \end{bmatrix}_{s}^{-} \left(\operatorname{Sia} \right)_{j}^{-} \left(\operatorname{R} \right)_{x} \\ \end{bmatrix}_{t}^{c} \\ \left\{ \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{a} \end{bmatrix}_{a}^{c} \left(\operatorname{Sia} \right)_{m}^{-} \left(\operatorname{R} \right)_{y} \\ \end{bmatrix}_{t}^{c} \\ \left\{ \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{a} \end{bmatrix}_{a}^{c} \left(\operatorname{Sia} \right)_{m}^{-} \left(\operatorname{R} \right)_{y} \\ \end{bmatrix}_{t}^{c} \\ \left\{ \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{a} \end{bmatrix}_{a}^{c} \left(\operatorname{Sia} \right)_{m}^{-} \left(\operatorname{R} \right)_{y} \\ \end{bmatrix}_{t}^{c} \\ \left\{ \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{a} \end{bmatrix}_{a}^{c} \left(\operatorname{Sia} \right)_{m}^{-} \left(\operatorname{R} \right)_{y} \\ \end{bmatrix}_{t}^{c} \\ \left\{ \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{a} \end{bmatrix}_{a}^{c} \left(\operatorname{Sia} \right)_{m}^{-} \left(\operatorname{R} \right)_{y} \\ \end{bmatrix}_{t}^{c} \\ \left\{ \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{a} \end{bmatrix}_{a}^{c} \left(\operatorname{Sia} \right)_{m}^{-} \left(\operatorname{R} \right)_{y} \\ \end{bmatrix}_{t}^{c} \\ \left\{ \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{a} \end{bmatrix}_{a}^{c} \left(\operatorname{Sia} \right)_{m}^{c} \left(\operatorname{R} \right)_{y} \\ \end{bmatrix}_{t}^{c} \\ \left\{ \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{a} \end{bmatrix}_{a}^{c} \left(\operatorname{Sia} \right)_{m}^{c} \left(\operatorname{R} \right)_{y} \\ \end{bmatrix}_{t}^{c} \\ \left\{ \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{a} \end{bmatrix}_{a}^{c} \left(\operatorname{Sia} \right)_{m}^{c} \left(\operatorname{R} \right)_{y} \\ \end{bmatrix}_{t}^{c} \\ \left\{ \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{a} \end{bmatrix}_{a}^{c} \left(\operatorname{Sia} \right)_{m}^{c} \left(\operatorname{R} \right)_{y} \\ \end{bmatrix}_{t}^{c} \\ \left\{ \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{a} \end{bmatrix}_{a}^{c} \left(\operatorname{Sia} \right)_{m}^{c} \left(\operatorname{R} \right)_{y} \\ \end{bmatrix}_{t}^{c} \\ \left\{ \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{a} \end{bmatrix}_{a}^{c} \left(\operatorname{Sia} \right)_{m}^{c} \left(\operatorname{R} \right)_{y} \\ \end{bmatrix}_{t}^{c} \\ \left\{ \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{a} \end{bmatrix}_{a}^{c} \left(\operatorname{Sia} \right)_{m}^{c} \left(\operatorname{R} \right)_{y} \\ \left\{ \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{a} \end{bmatrix}_{a}^{c} \left(\operatorname{Sia} \right)_{m}^{c} \left(\operatorname{R} \right)_{y} \\ \right\}_{t}^{c} \\ \left\{ \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{a} \end{bmatrix}_{a}^{c} \left(\operatorname{Sia} \right)_{m}^{c} \left(\operatorname{R} \right)_{y} \\ \left\{ \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{a} \end{bmatrix}_{a}^{c} \left(\operatorname{Sia} \right)_{m}^{c} \left(\operatorname{R} \right)_{y} \\ \left\{ \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{a} \end{bmatrix}_{a}^{c} \left(\operatorname{Sia} \right)_{m}^{c} \left(\operatorname{R} \right)_{y} \\ \left\{ \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{a} \end{bmatrix}_{a}^{c} \left(\operatorname{Sia} \right)_{m}^{c} \left(\operatorname{R} \right)_{y} \\ \left\{ \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{a} \end{bmatrix}_{a}^{c} \left(\operatorname{Sia} \right)_{m}^{c} \left(\operatorname{Sia} \right)_{m}^{c} \left(\operatorname{R} \right)_{y} \\ \left\{ \begin{bmatrix} \operatorname{GlcNAc-(Gal)}_{a} \end{bmatrix}_{a}^{c} \left(\operatorname{Sia} \right)_{m}^{c} \left($$

a-d, i, q-u (independently selected) = 0 or 1. e-h (independently selected) = 0 to 6. j-m (independently selected) = 0 to 100. v-y = 0; R = polymer.

FIG. 38A

CHO, BHK, 293 cells, Vero or transgenic animal expressed α_1 antitrypsin. a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y = 0.

```
    Sialidase
    CMP-SA-PEG (16 mol eq),
ST3Gal3
```

a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y (independently selected) = 1, when j-m (independently selected) is 1; R = PEG.

FIG. 38B

CHO, BHK, 293 cells, Vero or transgenic animal expressed α_1 antitrypsin. a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y = 0.

 Sialidase
 CMP-SA-PEG (1.2 mol eq), ST3Gal3
 CMP-SA (16 mol eq), ST3Gal3

a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y (independently selected) = 0 or 1; R = PEG.

FIG. 38C

```
CHO, BHK, 293 cells, Vero or transgenic animal expressed alpha-1 antitrypsin.
a-d, i-m, q-u (independently selected) = 0 or 1;
c-h = 1; v-y = 0.

1. Sialidase
2. CMP-SA-PEG (16 mol eq),
ST3Gal3

a-d, i-m, q-u (independently selected) = 0 or 1;
c-h = 1; v-y (independently selected) = 0 or 1;
R = PEG.
```

FIG. 38D

```
CHO, BHK, 293 cells, Vero or transgenic animal expressed \alpha_1-antitrypsin.

a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y = 0.

1. CMP-SA-levulinate, ST3Gal3, buffer, salt
v 2. H<sub>4</sub>N<sub>2</sub>-PEG

a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y (independently selected) = 0 or 1;
R = PEG.
```

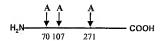
FIG. 38E

CHO, BHK, 293 cells, Vero expressed α_1 -antitrypsin. a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y = 0.

1. CMP-SA, α2,8-ST

a-d, i, q-u (independently selected) = 0 or 1; e-h = 1; j-m (independently selected) = 0-20; v-y (independently selected) = 0.

FIG. 38F



$$\mathbf{A} \leftarrow \begin{bmatrix} [\operatorname{GlcNAc-(Gal)_{a}]_{a}^{-}}(\operatorname{Sia})_{j}^{-}(R)_{v} \end{bmatrix} \\ + \begin{bmatrix} [\operatorname{GlcNAc-(Gal)_{a}]_{a}^{-}}(\operatorname{Sia})_{j}^{-}(R)_{v} \end{bmatrix} \\ + \begin{bmatrix} [\operatorname{GlcNAc-(Gal)_{a}]_{a}^{-}}(\operatorname{Sia})_{j}^{-}(\operatorname{Sia})_{j}^{-}(R)_{v} \end{bmatrix} \\ + \begin{bmatrix} [\operatorname{GlcNAc-(Gal)_{a}]_{a}^{-}}(\operatorname{Sia})_{j}^{-}(R)_{y} \end{bmatrix} \\ + \begin{bmatrix} [\operatorname{GlcNAc-(Gal)_{a}]_{a}^{-}}(\operatorname{Sia})_{a}^{-}(R)_{y} \end{bmatrix} \\ + \begin{bmatrix} [\operatorname{GlcNAc-(Gal)_{a}]_{a}^{-}}(\operatorname{Sia})_{a}^{-}(R)_{y} \end{bmatrix} \\ + \begin{bmatrix} [\operatorname{GlcNAc-(Gal)_{a}]_{a}^{-}}(\operatorname{Sia})_{a}^{-}(R)_{a}^{-}(R)_{a}^{-}(R)_{a}^{-}(R)_{a}^{-}(R)_{a}^{-}(R)_{a}^{-}(R)_{a}^{-}(R)_{a}^{-}(R)_{a}^{-}(R)_{a}^{-}(R)_{a}^{-}(R)_{a}^{-}(R)_{a}^{-}($$

a-d, i, n, p-u (independently selected) = 0 or 1.
e-h (independently selected) = 0 to 6.
j-m (independently selected) = 0 to 100.
v-y = 0;
R = modifying group, mannose, oligo-mannose;
R' = H, glycosyl residue, modifying group, glycoconjugate.

FIG. 38G

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Insect or fungi cell expressed α_1 -antitrypsin. a-d, f, h, j-m, s, u, v-y = 0; e, g, i, q, r, t (independently selected) = 0 or 1.

```
1. GNT's 1,2,4,5, UDP-GlcNAc
2. Galactosyltransferase, UDP-Gal-PEG
```

```
a-i, q-u (independently selected) = 0 or 1; j-m = 0; v-y (independently selected) = 1, when e-h (independently selected) is 1; R = PEG.
```

FIG. 38H

```
Yeast expressed \alpha_1-antitrypsin.

a-m = 0; q-y (independently selected) = 0 to 1;

p = 1; R (branched or linear) = Man, oligomannose.
```

- Endoglycanase
- 2. Galactosyltransferase, UDP-Gal
- 3. CMP-SA-PEG, ST3Gal3

a-m, p-y = 0; n (independently selected) = 0 or 1; R' = -Gal-Sia-PEG.

FIG. 381

CHO, BHK, 293 cells, Vero expressed α_1 -antitrypsin. a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y = 0.

- CMP-SA-linker-Gal-UDP, ST3Gal3
- 2. Galactosyltransferase, transferrin treated with endoglycanase

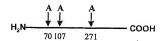
```
a-m, q-u (independently selected) = 0 or 1;

p = 1; n = 0;

v-y (independently selected) = 0 or 1;

R = linker-transferrin.
```

FIG. 38J



$$(Fuc)_{i} \\ A \leftarrow GlcNAc - GlcNAc - Man \\ (R')_{p} \\ (R')_{q} \\ (R$$

a-d, i, n-u (independently selected) = 0 or 1.

e-h (independently selected) = 0 to 4.

j-m (independently selected) = 0 to 20.

R = polymer;

R', R" (independently selected) = sugar, glycoconjugate.

FIG. 38K

```
Yeast expressed alpha-1 antitrypsin.
a-h, i-m, p, q = 0;
R (independently selected) = mannose, oligomannose, polymannose;
r-u, v-y (independently selected) = 0 or 1; n, o = 1.
```

endoglycanase

▼ 2. Galactosyltransferase, UDP-Gal-PEG

```
a-h, i-o, q, r-u, v-y = 0; p = 1.
R" = Gal-PEG.
```

FIG. 38L

```
Plant expressed alpha-1 antitrypsin.
a-d, f, h, j- m, s, u, v-y = 0;
e, g, i, q, r, t (independently selected) = 0 or 1;
n=1; \mathbb{R}^2 = xylose
```

- 1. hexosaminidase,
- alpha mannosidase and xylosidase
 GlcNAc transferase, UDP-GlcNAc-PEG
- To the manufacture, CD1 "Gleivic-1 Ex

```
a-d, f, h, j-n, s, u, v-y = 0;
e, g, i, r, t (independently selected) = 0;
q = 1; R' = GlcNAc-PEG.
```

FIG. 38M

```
CHO, BHK, 293 cells, Vero, transgenic animal expressed \alpha, antitrypsin.

a-h, i-o, r-u (independently selected) = 0 or 1; p, q, v-y = 0.

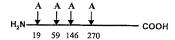
1. CMP-SA-PEG, ST3Gal3

a-h, i-o, r-u (independently selected) = 0 or 1;
```

p, q = 0; v-y (independently selected) = 0 or 1;

FIG. 38N

R = PEG.



$$A \leftarrow \begin{array}{l} \text{(Fuc)}_{i} \\ \text{(GlcNAc-(Gal))}_{i} \\ \text{(GlcNAc-GlcNAc-Man)} \\ \text{(GlcNAc-GlcNAc-Man)} \\ \text{(IGlcNAc-(Gal))}_{i} \\ \text{(Sia)}_{i} \\ \text{(Sia)}_{i} \\ \text{(R)}_{w} \\ \text{(Sia)}_{i} \\ \text{(Sia)}_{i} \\ \text{(R)}_{w} \\ \text{(Sia)}_{i} \\ \text{(Sia)}_{m} \\ \text{(R)}_{y} \\ \text{(R)}_{w} \\ \text{($$

a-d, i, q-u (independently selected) = 0 or 1. e-h (independently selected) = 0 to 6. j-m (independently selected) = 0 to 100. v-y = 0; R = polymer.

FIG. 39A

```
CHO, BHK, 293 cells, Vero expressed Cerezyme a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y = 0.
```

```
    Sialidase
    CMP-SA-PEG (16 mol eq),
ST3Gal3
```

```
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y (independently selected) = 1,
when j-m (independently selected) is 1;
R = PEG.
```

FIG. 39B

```
CHO, BHK, 293 cells, Vero expressed Cerezyme. a-d, i-m, q-u (independently selected) = 0 or 1; e-h=1; v-y=0.
```

- Sialidase
 CMP-SA-M-6-P (1.2 mol eq),
- ST3Gal3
 3. CMP-SA (16 mol eq), ST3Gal3
- 5. CMI -SA (10 moi eq), S13Gai.

a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y (independently selected) = 0 or 1; R = mannose-6-phosphate

FIG. 39C

```
CHO, BHK, 293 cells, Vero expressed Cerezyme.
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y = 0.

1. Sialidase
2. CMP-SA-PEG (16 mol ec).
```

```
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y (independently selected) = 0 or 1;
R = Mannose-6-phosphate
```

ST3Gal3
3. CMP-SA, ST3Gal3

FIG. 39D

```
CHO, BHK; 293 cells, Vero expressed Cerezyme.
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y = 0.
```

```
1. CMP-SA-levulinate, ST3Gal3,
buffer, salt
2. H<sub>4</sub>N<sub>2</sub>-spacer-M-6-P or clustered M-6-P
```

```
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y (independently selected) = 0 or 1;
R = M-6-P or clustered M-6-P
```

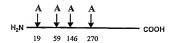
FIG. 39F

CHO, BHK, 293 cells, Vero expressed Cerezyme. a-d, i-m, q-u (independently selected) = 0 or 1; e-h=1; v-y=0.

1. CMP-SA, α2,8-ST

a-d, i, q-u (independently selected) = 0 or 1; e-h = 1; j-m (independently selected) = 0-20; v-y (independently selected) = 0.

FIG. 39F



$$\mathbf{A} \leftarrow \begin{bmatrix} [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{a}]_{a}^{-} & (\mathrm{Sia})_{j}^{-} & (\mathrm{R})_{v} \\ [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{a}]_{a}^{-} & (\mathrm{Sia})_{j}^{-} & (\mathrm{R})_{v} \end{bmatrix}_{q} \\ [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{a}]_{a}^{-} & (\mathrm{Sia})_{a}^{-} & (\mathrm{R})_{w} \end{bmatrix}_{q} \\ [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{a}]_{b}^{-} & (\mathrm{Sia})_{m}^{-} & (\mathrm{R})_{y} \end{bmatrix}_{q} \\ [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{a}]_{b}^{-} & (\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{a}]_{b}^{-} & (\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{a})_{a} \\ [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{a}]_{b}^{-} & (\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{a})_{a} \\ [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{a}]_{a} \\ [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{a}]_{a} \\ [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{a}]_{a} \\ [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{a}]_{a} \\ [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{a}]_{a} \\ [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{a}]_{a} \\ [\mathrm{$$

a-d, i, n, p-u (independently selected) = 0 or 1.
e-h (independently selected) = 0 to 6.
j-m (independently selected) = 0 to 100.
v-y = 0;
R = modifying group, mannose, oligo-mannose;
R' = H, glycosyl residue, modifying group,
glycoconjugate.

FIG. 39G

```
\label{eq:linear_constraints} \begin{split} & \text{Insect cell expressed Cerezyme.} \\ & \text{a-d, } f, h, j\text{-m, } s, u, v\text{-y} = 0; \\ & \text{e, } g, i, q, r, \text{ t (independently selected)} = 0 \text{ or } 1. \end{split}
```

```
1. GNT's 1,2,4,5, UDP-GlcNAc
2. Galactosyltransferase, UDP-Gal-PEG
```

```
a-i, q-u (independently selected) = 0 or 1;
j-m = 0;
v-y (independently selected) = 1,
when e-h (independently selected) is 1;
R = PEG.
```

FIG. 39H

```
Yeast expressed Cerezyme.

a-m=0; q-y (independently selected) = 0 to 1;

p=1; R (branched or linear) = Man, oligomannose.
```

```
1. Endoglycanase
2. Galactosyltransferase, UDP-Gal
▼ 3. CMP-SA-PEG, ST3Gal3
```

```
a-m, p-y = 0; n (independently selected) = 0 or 1; R' = -Gal-Sia-PEG.
```

FIG. 391

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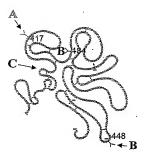
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CHO, BHK, 293 cells, Vero expressed Cerezyme. a-d, i-m, q-u (independently selected) = 0 or 1; e-h=1; v-y=0.

- CMP-SA-linker-SA-CMP, ST3Gal3
- 2. ST3Gal3, desialylated transferrin.
- 3. CMP-SA, ST3Gal3

a-m, q-u (independently selected) = 0 or 1; p = 1; n = 0; v-y (independently selected) = 0 or 1; R = linker-transferrin.

FIG. 39J



$$B \leftarrow \begin{array}{l} \text{(Fuc)}_{i} \\ B \leftarrow \begin{array}{l} \text{GlcNAc-Gal)}_{s}_{l}_{c} \cdot (\text{Sa)}_{j} \cdot (\text{R})_{v} \end{array} \Big]_{r} \\ \text{(R')}_{o} \end{array} \\ \text{Man} \left[\begin{array}{l} \text{[GlcNAc-(Gal)}_{s}]_{e}^{-} \cdot (\text{Sia})_{j} \cdot (\text{R})_{v} \end{array} \right]_{r} \\ \text{([GlcNAc-(Gal)}_{e}]_{g}^{-} \cdot (\text{Sia})_{i} \cdot (\text{R})_{x} \end{array} \Big]_{r} \\ \text{Man} \left[\begin{array}{l} \text{[GlcNAc-(Gal)}_{d}]_{h}^{-} \cdot (\text{Sia})_{m}^{-} \cdot (\text{R})_{y} \end{array} \right]_{r} \\ \text{[[GlcNAc-(Gal)}_{d}]_{h}^{-} \cdot (\text{Sia})_{m}^{-} \cdot (\text{R})_{y} \end{array} \right]_{r} \\ \text{([GlcNAc-(Gal)}_{d}]_{h}^{-} \cdot (\text{Sia})_{m}^{-} \cdot (\text{R})_{y} \end{array} \Big]_{r} \\ \text{([GlcNAc-(Gal)}_{d}]_{h}^{-} \cdot (\text{Sia})_{m}^{-} \cdot (\text{R})_{y} \end{array} \Big]_{r} \\ \text{([GlcNAc-(Gal)}_{d}]_{h}^{-} \cdot (\text{Sia})_{m}^{-} \cdot (\text{R})_{y} \\ \text{([GlcNAc-(Gal)}_{d}]_{h}^{-} \cdot (\text{R})_{y} \\ \text{([GlcNAc-(Gal)}_{d})_{h}^{-} \cdot (\text{R})_{h}^{-} \cdot (\text{R})_{h}^{-} \cdot (\text{R})_{h}^{-} \\ \text{([GlcNAc-(Gal)}_{d}]_{h}^{-} \cdot (\text{R})_{h}^{-} \cdot (\text{R})_{h}^{-} \\ \text{([GlcNAc-(Gal)}_{d}]_{h}^{-} \cdot (\text{R})_{h}^{-} \cdot (\text{R})_{h}^{-} \cdot (\text{R})_{h}^{-} \\ \text{([GlcNAc-(Gal)}_{d}]_{h}^{-} \cdot (\text{R})_{h}^{-} \cdot (\text{R})_{h}^{-} \cdot (\text{R})_{h}^{-} \\ \text{([GlcNAc-(Gal)}_{d}]_{h}^{-} \cdot (\text{R})_{h}^{-} \cdot (\text{R})_{h}^{-} \cdot (\text{R})_{h}^{-} \cdot (\text{R})_{h}^{-} \\ \text{([GlcNAc-(Gal)}_{d}]_{h$$

$$C \longleftarrow \text{-(Fuc)}_{0\text{-}1} \qquad A \longleftarrow \text{-GlcNAc-GlcNAc-Man} \qquad \begin{array}{c} \text{Man-[Man]}_{0\text{-}12} \\ \text{Man} \end{array} \begin{array}{c} \text{[Man]}_{0\text{-}6} \\ \text{[Man]}_{0\text{-}6} \end{array}$$

a-d, i, n-u (independently selected) = 0 or 1. e-h (independently selected) = 0 to 4. j-m (independently selected) = 0 to 20. R = polymer; R' = sugar, glycoconjugate.

FIG. 40A

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```
CHO, BHK, 293 cells, Vero expressed tPA
a-g, n = 1; h = 1 to 3;
j-m, i, (independently selected) = 0 or 1;
r-u (independently selected) = 0 to 1; o, v-y = 0.
```

```
1. Mannosidase(s), sialidase
2. GNT1,2 (4 and/or 5) UDP-GlcNAc
3. Gal transferase, UDP-Gal

4. CMP-SA-PEG, ST3Gal3
```

```
A = B; a-g, n = 1; h = 1 to 3;
i, r-u (independently selected) = 0 or 1;
o = 0; j-m, v-y (independently selected) = 0 or 1;
R = PEG
```

FIG. 40B

```
Insect or fungi cell expressed tPA
A = B; a-d, f, h, j-o, s, u, v-y = 0;
e, g, i, n, r, t (independently selected) = 0 or 1.
```

```
1. GNT's 1&2, UDP-GlcNAc
2. Galactosyltransferase, UDP-Gal

▼ 3. CMP-SA-PEG. ST3Gal3
```

```
\begin{split} A=B; & b,d,\ f,\ h,\ k,m,o,s,u,w,y=0;\\ a,c,e,g,\ i,\ r,\ t & (independently\ selected)=0\ or\ 1;\\ n=1; & j,l,v,x\ (independently\ selected)=0\ or\ 1;\\ R=PEG. \end{split}
```

FIG. 40C

Yeast expressed tPA B = A; i = 0.

- 1. endoglycanase
- 2. Galactosyltransferase, UDP-Gal-PEG

A = B; a-n, r-y = 0; o = 1; R' = Gal-PEG.

FIG. 40D

Insect or fungi cell expressed tPA
A = B; a-d, f, h, j-o, s, u, v-y = 0;
e, g, i, n, r, t (independently selected) = 0 or 1.

- alpha and beta mannosidases
- 2. Galactosyltransferase, UDP-Gal-PEG

A = B; a-n, r-y = 0; o = 1; R' = Gal-PEG.

FIG. 40E

```
Insect or fungi cell expressed tPA

A = B; a-d, f, h, j-o, s, u, v-y = 0;
e, g, i, n, r, t (independently selected) = 0 or 1.
```

```
    GNT's 1&2, UDP-GlcNAc
    Galactosyltransferase, UDP-Gal-PEG
```

```
\begin{array}{lll} A=B; & b,\ d,\ f,\ h,\ j\text{-o},\ s,\ u,\ w,\ y=0;\\ a,\ c,\ e,\ g,\ i,\ r,\ t,\ v,\ x\ (independently\ selected)=0\ \mathrm{or}\ 1;\\ n=1;\ R=PEG. \end{array}
```

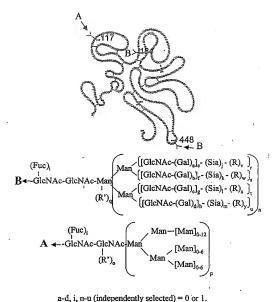
FIG. 40F

```
Insect or fingi cell expressed tPA A = B; a-d, f, h, j-o, s, u, v-y = 0; e, g, i, n, r, t (independently selected) = 0 or 1.
```

- GNT's 1 & 2, UDP-GlcNAc
 Galactosidase (synthetic enzyme)
- Galactosidase (synthetic enzyme), PEG-Gal-F.

```
A=B;\ b,d,\ f,\ h,\ j\text{-o},\ s,\ u,\ w,\ y=0; a, c, e, g, i, r, t, v, x (independently selected)=0 or 1; n=1; R=PEG.
```

FIG. 40G



a-d, 1, 1-u (independently selected) = 0 or 1.
e-h (independently selected) = 0 to 4.
j-m (independently selected) = 0 to 20.
R = polymer; R' = sugar, glycoconjugate.

FIG. 40H

```
NSO expressed tPA
A = B; a-m, r-u (independently selected) = 0 or 1;
n = 1; o, p, q, v-v = 0
```

```
1. sialidase, alpha-galactosidase
2. CMP-SA-levulinate, ST3Gal3,
```

```
A = B; a-m, r-y (independently selected) = 0 or 1;
n = 1; o, p, q = 0;
v-v (independently selected) = 1,
 when j-m (independently selected) is 1;
R = PEG.
```

FIG. 401

```
CHO, BHK, 293 cells, Vero expressed tPA
a-g, n, p = 1; h = 1 \text{ to } 3;
j-m, i, (independently selected) = 0 or 1;
r-u (independently selected) = 0 to 1; q, o, v-y=0.
```

- alpha and beta Mannosidases
 CMP-SA, ST3Gal3
- 3. Galactosyltransferase, UDP-Gal-PEG

```
a-g, n = 1; h = 1 to 3;
i, r-u (independently selected) = 0 or 1; o = 1;
q, p, v-y=0; j-m (independently selected) = 0 or 1;
R' = Gal-PEG
```

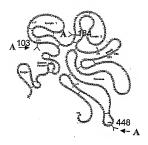
FIG. 40.1

Plant expressed tPA $A=B; \ a-d, f, h, j \cdot m, s, u \cdot v-y=0; \\ e, g, \ i, \ q, r, \ t (independently selected)=0 \ or \ 1; \\ n=1; \ R'=xylose$

- 1. hexosaminidase,
- alpha mannosidase and xylosidase
- 3. GlcNAc transferase, UDP-GlcNAc-PEG

A = B; a-d, f, h, j-n, s, u, v-y = 0; e, g, i, r, t (independently selected) = 0; q = 1; R' = GlcNAc-PEG.

FIG. 40K



$$\mathbf{A} \leftarrow \begin{bmatrix} (\operatorname{Fuc})_{i} & & & \\ -(\operatorname{GlcNAc-Glc})_{a}l_{r} & & (\operatorname{Sia})_{s}^{-} & (\operatorname{Sia})_{s}^{-} & (\operatorname{R})_{w} \\ -(\operatorname{GlcNAc-Glc})_{a}l_{r} & & (\operatorname{Sia})_{s}^{-} & (\operatorname{R})_{w} \end{bmatrix}_{s} \\ + (\operatorname{GlcNAc-Glc})_{a}l_{n} & & (\operatorname{Sia})_{s}^{-} & (\operatorname{R})_{w} \end{bmatrix}_{s} \\ + (\operatorname{GlcNAc-Glc})_{a}l_{n} & & (\operatorname{Sia})_{s}^{-} & (\operatorname{R})_{w} \end{bmatrix}_{u} \\ + (\operatorname{GlcNAc-Glc})_{a}l_{n} & & (\operatorname{Sia})_{m}^{-} & (\operatorname{R})_{y} \end{bmatrix}_{u} \\ + (\operatorname{GlcNAc-Glc})_{a}l_{n} & & (\operatorname{Glc})_{a}l_{n} & (\operatorname{Sia})_{m}^{-} & (\operatorname{R})_{y} \end{bmatrix}_{u} \\ + (\operatorname{GlcNAc-Glc})_{a}l_{n} & & (\operatorname{Glc})_{a}l_{n} & (\operatorname{Sia})_{m}^{-} & (\operatorname{R})_{y} \end{bmatrix}_{u} \\ + (\operatorname{GlcNAc-Glc})_{a}l_{n} & & (\operatorname{Glc})_{a}l_{n} & (\operatorname{Sia})_{m}^{-} & (\operatorname{R})_{y} \end{bmatrix}_{u} \\ + (\operatorname{GlcNAc-Glc})_{a}l_{n} & & (\operatorname{Glc})_{a}l_{n} & (\operatorname{Glc})_{a}l_{n} & (\operatorname{Glc})_{n} &$$

a-d, i, q-u (independently selected) = 0 or 1. e-h (independently selected) = 0 to 6. j-m (independently selected) = 0 to 100. $^{\prime}$ v-y = 0; R = polymer.

FIG. 40L

```
CHO, BHK, 293 cells, Vero expressed TNK tPA a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y = 0.
```

```
    Sialidase
    CMP-SA-PEG (16 mol eq),
ST3Gal3
```

```
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y (independently selected) = 1,
when j-m (independently selected) is 1;
R = PEG.
```

FIG. 40M

```
CHO, BHK, 293 cells, Vero expressed TNK tPA a-d, i-m, q-u (independently selected) = 0 or 1; e-h=1; v-y=0.
```

```
1. Sialidase
2. CMP-SA-PEG (1.2 mol eq),
ST3Gal3
3. CMP-SA (16 mol eq), ST3Gal3
```

```
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = l,; v-y (independently selected) = 0 or 1;
R = PEG.
```

FIG. 40N

NSO expressed TNK tPA a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y = 0; Sia (independently selected) = Sia or Gal.

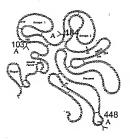
- Sialidase and α-galactosidase
 Galactosyltransferase, UDP-Gal
- ▼ 3. CMP-SA-PEG, ST3Gal3

a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y (independently selected) = 1, when j-m (independently selected) is 1; R = PEG.

FIG. 400

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$$\mathbf{A} \bullet \begin{bmatrix} [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{a}]_{a}^{-}(\mathrm{Sia})_{j}^{-}(R)_{v} \\]_{t} \\ \mathrm{GlcNAc\text{-}}(\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{b}]_{t}^{-}(\mathrm{Sia})_{k}^{-}(R)_{w} \end{bmatrix}_{t}^{t} \\ \mathbf{A} \bullet \begin{bmatrix} [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{b}]_{t}^{-}(\mathrm{Sia})_{k}^{-}(R)_{w} \\]_{t} \\ \mathrm{Man} \begin{bmatrix} [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{d}]_{a}^{-}(\mathrm{Sia})_{j}^{-}(R)_{y} \\ \end{bmatrix}_{t} \\ [[\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{d}]_{b}^{-}(\mathrm{Sia})_{m}^{-}(R)_{y} \end{bmatrix}_{u}^{t} \\ \mathbf{A} \bullet \begin{bmatrix} [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{d}]_{b}^{-}(\mathrm{Sia})_{j}^{-}(R)_{y} \\ [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{d}]_{b}^{-}(\mathrm{Sia})_{m}^{-}(R)_{y} \end{bmatrix}_{u}^{t} \\ \mathbf{A} \bullet \begin{bmatrix} [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{d}]_{b}^{-}(\mathrm{Sia})_{j}^{-}(R)_{y} \\ [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{d}]_{b}^{-}(\mathrm{Sia})_{m}^{-}(R)_{y} \end{bmatrix}_{t}^{t} \\ \mathbf{A} \bullet \begin{bmatrix} [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{d}]_{b}^{-}(\mathrm{Sia})_{j}^{-}(R)_{y} \\ [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{d}]_{b}^{-}(\mathrm{Sia})_{m}^{-}(R)_{y} \end{bmatrix}_{t}^{t} \\ \mathbf{A} \bullet \begin{bmatrix} [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{d}]_{b}^{-}(\mathrm{Sia})_{m}^{-}(R)_{y} \\ [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{d}]_{b}^{-}(\mathrm{Sia})_{m}^{-}(R)_{y} \end{bmatrix}_{t}^{t} \\ \mathbf{A} \bullet \begin{bmatrix} [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{d}]_{b}^{-}(\mathrm{Sia})_{m}^{-}(\mathrm{Sia})_{m}^{-}(R)_{y} \\ [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{d}]_{t}^{t} \\ \mathbf{A} \bullet \begin{bmatrix} [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{d}]_{b}^{-}(\mathrm{Gal})_{d} \\ [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{d}]_{t}^{-}(\mathrm{Gal})_{d} \\ [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{d}]_{t}^{t} \\ \mathbf{A} \bullet \begin{bmatrix} [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{d}]_{t}^{-}(\mathrm{Gal})_{d} \\ [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{d}]_{t}^{-}(\mathrm{Gal})_{d} \\ [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{d}]_{t}^{t} \\ \mathbf{A} \bullet \begin{bmatrix} [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{d}]_{t}^{-}(\mathrm{Gal})_{d} \\ [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{d}]_{t}^{-}(\mathrm{Gal})_{d} \\ [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{d}]_{t}^{t} \\ \mathbf{A} \bullet \begin{bmatrix} [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{d}]_{t}^{-}(\mathrm{Gal})_{d} \\ [\mathrm{GlcNAc\text{-}}(\mathrm{Gal})_{d}]_{t}^{-}(\mathrm{Gal})$$

a-d, i, q-u (independently selected) = 0 or 1. e-h (independently selected) = 0 to 6. j-m (independently selected) = 0 to 100. v-y = 0; R = polymer.

FIG. 40P

```
CHO, BHK, 293 cells, Vero expressed TNK tPA
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y = 0.

1. Sialidase
2. CMP-SA-PEG (16 mol eq),
ST3Gal3
3. CMP-SA, ST3Gal3

a-d, i-m, q-u (independently selected) = 0 or 1;
```

e-h=1; v-y (independently selected) = 0 or 1;

FIG. 40Q

R = PEG.

```
CHO, BHK, 293 cells, Vero expressed TNK tPA a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y = 0.
```

```
    CMP-SA-levulinate, ST3Gal3,
buffer, salt
    H<sub>4</sub>N<sub>2</sub>-PEG
```

```
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y (independently selected) = 0 or 1;
R = PEG.
```

FIG. 40R

CHO, BHK, 293 cells, Vero expressed TNK tPA a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; \mathbf{v} - \mathbf{y} = 0.

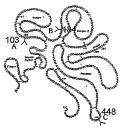
1. CMP-SA, α2,8-ST

a-d, i, q-u (independently selected) = 0 or 1; e-h = 1; j-m (independently selected) = 0-20; v-y (independently selected) = 0.

FIG. 40S

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$$\mathbf{A} \overset{\text{(R'')}_0}{\underset{\mid}{\text{GlcNAc-(Gal)}_a\mathbf{J_c^-(Sia)}_j^-(R)_w}} \underbrace{\mathbf{A}}^{\text{(R'')}_0} \underbrace{\mathbf{A}}^{\text{(R'')}_0} \underbrace{\mathbf{A}}^{\text{(IGlcNAc-(Gal)}_a\mathbf{J_c^-(Sia)}_j^-(R)_w} \underbrace{\mathbf{A}}^{\text{($$

a-d, i, n-y (independently selected) = 0 or 1.

e-h (independently selected) = 0 to 6.

j-m (independently selected) = 0 to 100.

R = modifying group, mannose, oligo-mannose;

R' = H, glycosyl residue, modifying group, glycoconjugate.

R" = glycosyl residue.

FIG. 40T

```
Insect cell expressed TNK tPA a-d, f, h, j-m, s, u, v-y = 0; e, g, i, q, r, t (independently selected) = 0 or 1.
```

```
1. GNT's 1,2,4,5, UDP-GlcNAc
2. Galactosyltransferase, UDP-Gal-PEG
```

```
a-i, q-u (independently selected) = 0 or 1;
j-m = 0; v-y (independently selected) = 1,
when e-h (independently selected) is 1;
R = PEG.
```

FIG. 40U

```
Yeast expressed TNK tPA a-m=0; q-y (independently selected) = 0 to 1; p=1; R (branched or linear) = Man, oligomannose.
```

```
    Endoglycanase
    Galactosyltransferase, UDP-Gal-PEG
```

```
a-m, p-y = 0; n (independently selected) = 0 or 1; R' = -Gal-PEG.
```

FIG. 40V

CHO, BHK, 293 cells, Vero expressed TNK tPA a-d, i-m, q-u (independently selected) = 0 or 1; e-h=1; v-y=0.

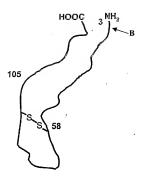
 CMP-SA-linker-Gal-UDP, ST3Gal3
 Galactosyltransferase, anti-TNF IG chimera produced in CHO.

a-m, r-u (independently selected) = 0 or 1; p, q = 1; n = 0; v-y (independently selected) = 0 or 1; R = linker-anti-TNF IG chimera protein.

FIG. 40W

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$$B \leftarrow \begin{bmatrix} (Sia)_b \\ -GalNAc-(Gal)_a-(Sia)_c-(R)_d \end{bmatrix}$$

a-c, e (independently selected) = 0 or 1; d=0; R= modifying group, mannose, oligomannose.

FIG. 41A

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```
CHO, BHK, 293 cells, Vero expressed IL-2
a-c, e (independently selected) = 0 or 1; d = 0

1. Sialidase
2. CMP-SA-PEG, ST3Gal1
a-d, e (independently selected) = 0 or 1;
```

FIG. 41B

R = PEG.

```
Insect cell expressed IL-2
a, e (independently selected) = 0 or 1;
b, e, d = 0.

1. Galactosyltransferase, UDP-Gal
```

- Galactosyltransferase, UDP-Gal
 CMP-SA-PEG, ST3Gal1
- a, c, d, e (independently selected) = 0 or 1; R = PEG.

FIG. 41C

```
E. coli expressed IL-2
a-e = 0.

1. GaiNAc Transferase, UDP-GaiNAc
2. CMP-SA-PEG, siatyltransferase

c, d, e (independently selected) = 0 or 1;
a, b = 0: R = PEG.
```

FIG. 41D

```
NSO expressed IL-2
a, e (independently selected) = 0 or 1;
b, c, d = 0

1. CMP-SA-levulinate, ST3Gal1
2. H_4N_2-PEG

a, c, d, e (independently selected) = 0 or 1;
b = 0; R = PEG.
```

FIG. 41E

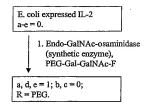


FIG. 41F

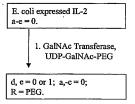


FIG. 41G

for some N-linked structures of A.

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2 peptides

A and A' - N-linked sites

B - O-linked sites

$$(\operatorname{Fuc})_{i} = (\operatorname{Gal})_{a} \cdot (\operatorname{Sia})_{j} \cdot (\operatorname{Sia})_{j} \cdot (\operatorname{R})_{v} \cdot (\operatorname{R})_{v} \cdot (\operatorname{Gal})_{a} \cdot (\operatorname{Sia})_{j} \cdot (\operatorname{R})_{v} \cdot (\operatorname{R})_{v} \cdot (\operatorname{Gal})_{a} \cdot (\operatorname{Sia})_{k} \cdot (\operatorname{R})_{v} \cdot (\operatorname{R})_{v} \cdot (\operatorname{Gal})_{k} \cdot ($$

A'-GicNAc-GicNAc

(R')

a-d, i, n-u (independently selected) = 0 or 1. aa, bb (independently selected) = 0 or 1. e-h (independently selected) = 0 to 6. j-m (independently selected) = 0 to 20. v-z=0; R = polymer, glycoconjugate.

FIG. 42A

```
CHO, BHK, 293s cells, Vero, MDCK, HEKC expressed Factor VIII. e-h = 1 to 4; aa, bb, a-d, j-m, i, n-u (independently selected) = 0 or 1; v-z = 0.
```

1. Sialidase
 ▼ 2. CMP-SA-PEG, ST3Gal3

```
e-h = 1 to 4;
aa, bb, a-d, i, n, q-u (independently selected) = 0 or 1;
o, p, z = 0; j-m, v-y (independently selected) = 0 or 1;
R = PEG.
```

FIG. 42B

```
CHO, BHK, 293S cells, Vero, MDCK, 293S, HEKC expressed Factor VIII. e-h = 1 to 4; aa, bb, a-d, j-m, i, n-u (independently selected) = 0 or 1; v-z = 0.
```

```
1. Sialidase
2. CMP-SA-PEG, ST3Gal3
3. ST3Gal1, CMP-SA
```

```
e-h = 1 to 4;
aa, bb, a-d, i, n, p-u (independently selected) = 0 or 1;
o, z = 0; j-m, v-y (independently selected) = 0 or 1;
R = PEG.
```

FIG. 42C

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```
CHO, BHK, 293s cells, Vero, MDCK, HEKC expressed Factor VIII. e-h= 1 to 4; aa, bb, a-d, j-m, i, n-u (independently selected)=0 or 1; v-z = 0.
```

1. CMP-SA-PEG, ST3Gal3

```
e-h = 1 to 4;
aa, bb, a-d, i, n-u (independently selected) = 0 or 1;
z = 0; j-m, v-y (independently selected) = 0 or 1;
R = PEG.
```

FIG. 42D

```
CHO, BHK, 293S cells, Vero, MDCK, HEKC expressed Factor VIII.
e-h = 1 to 4;
aa, bb, a-d, j-m, i, n-u (independently selected) 0 or 1;
v-z = 0.
```

1. CMP-SA-PEG, ST3Gal1

```
e-h = 1 to 4;
aa, bb, a-d, i, n-u (independently selected) = 0 or 1;
z = 0; j-m, v-y (independently selected) = 0 or 1;
R = PEG.
```

FIG. 42E

CHO, BHK, 293S cells, Vero, MDCK, HEKC expressed Factor VIII. e-h = 1 to 4; aa, bb, a-d, j-m, i, n-u (independently selected)=0 or 1; v-z = 0.

1. CMP-SA-PEG, α2,8-ST

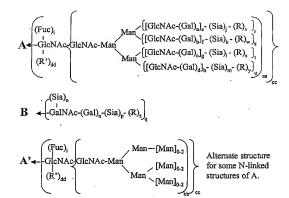
e-h = 1 to 4; aa, bb, a-d, i, n-y (independently selected) = 0 or 1; z = 0; j-m (independently selected) = 0 to 2; v-y (independently selected) = 1, when j-m (independently selected) is 2; R = PEG.

FIG. 42F

2 peptides

A OF A - N-linked sites

B - O-linked sites



a-d, i, n-u, (independently selected) = 0 or 1. aa, bb, cc, dd (independently selected) = 0 or 1. e-h (independently selected) = 0 to 6. j-m (independently selected) = 0 to 20. v-z = 0; R = modifying group, mannose, oligo-mannose.

R = modifying group, mannose, oligo-mannose R' = H, glycosyl residue, modifying group, glycoconjugate.

FIG. 42G

```
CHO, BHK, 293S cells, Vero, MDCK, HEKC expressed Factor VIII. e-h = 1 to 4; aa, bb, cc, a-d, j-m, i, n-u (independently selected) = 0 or 1; dd, v-z = 0.
```

1. CMP-SA-levulinate, ST3Gal3, 2. H₄N₂-PEG

```
e-h = 1 to 4;
aa, bb, cc, a-d, i, n-u (independently selected) = 0 or 1;
dd, z = 0; j-m, v-y (independently selected) = 0 or 1;
R = PEG.
```

FIG. 42H

```
CHO, BHK, 293S cells, Vero, MDCK, HEKC expressed Factor VIII. e-h = 1 to 4; as, bb, cc, a-d, j-m, i, n-u (independently selected) = 0 or 1; dd, v-z=0.
```

```
1. endo-H
2. galactosyltransferase, UDP-Gal-PEG
```

```
e-h = 1 to 4;
aa, bb, dd, a-d, i, j-u (independently selected) = 0 or 1;
cc, v-z=0; R' = -Gal-PEG.
```

FIG. 421

```
CHO, BHK, 293S cells, Vero, MDCK, HEKC expressed Factor VIII.
e-h = 1 to 4;
aa, bb, cc, a-d, j-m, i, n-u (independently selected) = 0 or 1;
dd, v-z = 0.
```

```
1. ST3Gal3, CMP-SA
2. endo-H
3. galactosyltransferase, UDP-Gal-PEG
```

e-h=1 to 4; aa, bb, dd, a-d, i, j-u (independently selected) = 0 or 1; cc, v-z=0; R'=-Gal-PEG.

FIG. 42J

```
CHO, BHK, 293S cells, Vero, MDCK, HEKC expressed Factor VIII. e-h = 1 to 4; aa, bb, cc, a-d, j-m, i, n-u (independently selected) = 0 or 1; dd, v-z = 0.
```

```
1. mannosidases
2. GNT 1 & 2, UDP-GlcNAc
```

3. galactosyltransferase, UDP-Gal-PEG

```
e-h = 1 to 4;
aa, a-d, i, j-y (independently selected) = 0 or 1;
bb, cc, dd, z = 0; R = PEG.
```

FIG. 42K

```
CHO, BHK, 293S cells, Vero, MDCK, HEKC expressed Factor VIII. e-h = 1 to 4; aa, bb, cc, a-d, j-m, i, n-u (independently selected) = 0 or 1; dd, v-z = 0.
```

- 1. mannosidases
- 2. GNT-1,2, 4 & 5; UDP-GicNAc
- ↓ 3. galactosyltransferase, UDP-Gal
 4. ST3Gal3, CMP-SA

```
e-h = 1 to 4;
aa, bb, cc, a-d, i, j-q (independently selected) = 0 or 1;
dd, v-z = 0.
```

FIG. 42L

```
CHO, BHK, 293S cells, Vero, MDCK, HEKC expressed Factor VIII. e-h = 1 to 4; aa, bb, cc, a-d, j-m, i, n-u (independently selected) = 0 or 1; dd, v-z = 0.
```

```
    1. mannosidases
    2. GNT-1, ÚDP-GlcNAc-PEG
```

```
e-h = 0 to 4;
aa, a-d, i, j-y (independently selected) = 0 or 1;
bb, cc, dd, z = 0.
```

FIG. 42M



$$\mathbf{A} \leftarrow \begin{bmatrix} [GlcNAc\text{-}(Gal)_{a}]_{a}^{-} (Sia)_{a}^{-} (R)_{v} \\ [GlcNAc\text{-}(Gal)_{b}]_{f}^{-} (Sia)_{k}^{-} (R)_{w} \end{bmatrix}_{t}^{t} \\ \mathbf{A} \leftarrow \begin{bmatrix} [GlcNAc\text{-}(Gal)_{b}]_{f}^{-} (Sia)_{k}^{-} (R)_{w} \\ [GlcNAc\text{-}(Gal)_{b}]_{g}^{-} (Sia)_{f}^{-} (R)_{x} \end{bmatrix}_{t}^{t} \\ \mathbf{Man} \begin{bmatrix} [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{y} \\ [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{y} \end{bmatrix}_{u}^{t} \\ \mathbf{Man} \begin{bmatrix} [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{y} \\ [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{y} \end{bmatrix}_{u}^{t} \\ \mathbf{Man} \begin{bmatrix} [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{y} \\ [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{y} \end{bmatrix}_{u}^{t} \\ \mathbf{Man} \begin{bmatrix} [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{y} \\ [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{y} \end{bmatrix}_{u}^{t} \\ \mathbf{Man} \begin{bmatrix} [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{y} \\ [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{y} \end{bmatrix}_{u}^{t} \\ \mathbf{Man} \begin{bmatrix} [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{y} \\ [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{y} \end{bmatrix}_{u}^{t} \\ \mathbf{Man} \begin{bmatrix} [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{y} \\ [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{y} \end{bmatrix}_{u}^{t} \\ \mathbf{Man} \begin{bmatrix} [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{y} \\ [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{y} \end{bmatrix}_{u}^{t} \\ \mathbf{Man} \begin{bmatrix} [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{y} \\ [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{y} \end{bmatrix}_{u}^{t} \\ \mathbf{Man} \begin{bmatrix} [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{y} \\ [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{y} \end{bmatrix}_{u}^{t} \\ \mathbf{Man} \begin{bmatrix} [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{w} \\ [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{w} \\ \mathbf{Man} \begin{bmatrix} [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{w} \\ [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{w} \\ \mathbf{Man} \begin{bmatrix} [GlcNAc\text{-}(Gal)_{d}]_{h}^{-} (Sia)_{m}^{-} (R)_{w} \\ \mathbf{Man} \end{bmatrix}_{u}^{-} \begin{bmatrix} [GlcNAc\text{-}(Gal$$

a-d, i, q-u (independently selected) = 0 or 1. e-h (independently selected) = 0 to 6. j-m (independently selected) = 0 to 100. v-y = 0; R = polymer.

FIG. 43A

```
CHO, BHK, 293 cells, Vero expressed Urokinase. a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y=0.
```

 Sialidase
 CMP-SA-PEG (16 mol eq), ST3Gal3

```
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y (independently selected) = 1,
when j-m (independently selected) is 1;
R = PEG.
```

FIG. 43B

```
CHO, BHK, 293 cells, Vero expressed Urokinase. a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y = 0.
```

```
1. Sialidase
2. CMP-SA-PEG (1.2 mol eq),
ST3Gal3
3. CMP-SA (16 mol eq), ST3Gal3
```

```
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y (independently selected) = 0 or 1;
R = PEG.
```

FIG. 43C

```
CHO, BHK, 293 cells, Vero expressed Urokinase. a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y = 0.
```

```
    Sialidase
    CMP-SA-PEG (16 mol eq),
ST3Gal3
```

a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y (independently selected) = 0 or 1; R = PEG.

FIG. 43D

```
CHO, BHK, 293 cells, Vero expressed Urokinase. a-d, i-m, q-u (independently selected) = 0 or 1; e-h=1; v-y=0.
```

```
    CMP-SA-levulinate, ST3Gal3,
buffer, salt
    H<sub>a</sub>N<sub>2</sub>-PEG
```

```
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y (independently selected) = 0 or 1;
R = PEG.
```

FIG. 43E

```
CHO, BHK, 293 cells, Vero expressed Urokinase.
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y = 0.

1. CMP-SA, α2,8-ST

a-d, i, q-u (independently selected) = 0 or 1;
e-h = 1;
j-m (independently selected) = 0-20;
```

v-y (independently selected) = 0.

FIG. 43F

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$$A \leftarrow \left(\begin{array}{c} \text{Fuc} j_i \\ \text{GlcNAc-Gal} j_{a_i} \text{-} \left(\text{Sia} j_i \text{-} \left(\text{Ri} j_i \right)_s \right) \\ \text{GlcNAc-Gal} j_{a_i} \text{-} \left(\text{Sia} j_i \text{-} \left(\text{Ri} j_i \right)_s \right) \\ \text{GlcNAc-Man} \\ \text{Man} \left(\begin{array}{c} \text{[GlcNAc-(Gal)_a]_e} \text{-} \left(\text{Sia} j_i \text{-} \left(\text{Ri} j_i \right)_s \right) \\ \text{GlcNAc-(Gal)_a]_e} \text{-} \left(\text{Sia} j_i \text{-} \left(\text{Ri} j_i \right)_s \right) \\ \text{GlcNAc-(Gal)_a]_e} \text{-} \left(\text{Sia} j_i \text{-} \left(\text{Ri} j_i \right)_s \right) \\ \text{GlcNAc-(Gal)_a]_e} \text{-} \left(\text{Sia} j_i \text{-} \left(\text{Ri} j_i \right)_s \right) \\ \text{GlcNAc-(Gal)_a]_e} \text{-} \left(\text{Sia} j_i \text{-} \left(\text{Ri} j_i \right)_s \right) \\ \text{GlcNAc-Gal)_a} \text{-} \left(\text{Ri} j_i \text{-} \left(\text{Ri} j_i \right)_s \right) \\ \text{GlcNAc-(Gal)_a} \text{-} \left(\text{Ri} j_i \right)_s \right) \\ \text{GlcNAc-(Gal)_a} \text{-} \left(\text{Ri} j_i \text{-} \left(\text{Ri} j_i \right)_s \right) \\ \text{GlcNAc-(Gal)_a} \text{-} \left(\text{Ri} j_i \text{-} \left(\text{Ri} j_i \right)_s \right) \\ \text{GlcNAc-(Gal)_a} \text{-} \left(\text{Ri} j_i \text{-} \left(\text{Ri} j_i \right)_s \right) \\ \text{GlcNAc-(Gal)_a} \text{-} \left(\text{Ri} j_i \text{-} \left(\text{Ri} j_i \right)_s \right) \\ \text{GlcNAc-(Gal)_a} \text{-} \left(\text{Ri} j_i \text{-} \left(\text{Ri} j_i \right)_s \right) \\ \text{GlcNAc-(Gal)_a} \text{-} \left(\text{Ri} j_i \text{-} \left(\text{Ri} j_i \right)_s \right) \\ \text{GlcNAc-(Gal)_a} \text{-} \left(\text{Ri} j_i \text{-} \left(\text{Ri} j_i \right)_s \right) \\ \text{GlcNAc-(Gal)_a} \text{-} \left(\text{Ri} j_i \text{-} \left(\text{Ri} j_i \right)_s \right) \\ \text{GlcNAc-(Gal)_a} \text{-} \left(\text{Ri} j_i \text{-} \left(\text{Ri} j_i \right)_s \right) \\ \text{GlcNAc-(Gal)_a} \text{-} \left(\text{Ri} j_i \text{-} \left(\text{Ri} j_i \right)_s \right) \\ \text{GlcNAc-(Gal)_a} \text{-} \left(\text{Ri} j_i \text{-} \left(\text{Ri} j_i \right)_s \right) \\ \text{GlcNAc-(Gal)_a} \text{-} \left(\text{Ri} j_i \text{-} \left(\text{Ri} j_i \right)_s \right) \\ \text{GlcNAc-(Gal)_a} \text{-} \left(\text{Ri} j_i \text{-} \left(\text{Ri} j_i \right)_s \right) \\ \text{GlcNAc-(Gal)_a} \text{-} \left(\text{Ri} j_i \text{-} \left(\text{Ri} j_i \right)_s \right) \\ \text{GlcNAc-(Gal)_a} \text{-} \left(\text{Ri} j_i \text{-} \left(\text{Ri} j_i \right)_s \right) \\ \text{GlcNAc-(Gal)_a} \text{-} \left(\text{Ri} j_i \right)_s \\ \text{GlcNAc-(Gal)_a} \\ \text{GlcNAc-(Gal)_a} \text{-} \left(\text{Ri} j_i \right)_s \\ \text{GlcNAc-(Gal)_a} \\ \text{GlcNAc-(Gal)_a} \text{-} \left(\text{Ri} j_i \right)_s \\ \text{GlcNAc-(Gal)_a} \\ \text{$$

a-d, i, n, p-u (independently selected) = 0 or 1.
e-h (independently selected) = 0 to 6.
j-m (independently selected) = 0 to 100.
v-y = 0;
R = modifying group, mannose, oligo-mannose;
R' = H, glycosyl residue, modifying group,
glycoconjugate.

FIG. 43G

```
Insect cell expressed Urokinase.
a-d, f, h, j-n, s, u, v-y = 0;
e, g, i, q, r, t (independently selected) = 0 or 1.
```

```
1. GNT's 1,2,4,5, UDP-GlcNAc
2. Galactosyltransferase, UDP-Gal-PEG
```

```
a-i, q-u (independently selected) = 0 or 1;
j-n = 0; v-y (independently selected) = 1,
when e-h (independently selected) is 1;
R = PEG.
```

FIG. 43H

```
Yeast expressed Urokinase.

a-n=0;

q-y (independently selected) = 0 to 1;

p=1; R (branched or linear) = Man, oligomannose.
```

```
    Endoglycanase
    Galactosyltransferase, UDP-Gal
    CMP-SA-PEG, ST3Gal3
```

```
a-m, p-y = 0; n (independently selected) = 0 or 1; R' = -Gal-Sia-PEG.
```

FIG. 431

```
CHO, BHK, 293 cells, Vero expressed Urokinase.
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; n, v-y = 0.
```

- CMP-SA-linker-SA-CMP, ST3Gal3
- ST3Gal1, desialylated Urokinase produced in CHO.
- ↓ 3. CMP-SA, ST3Gal3, ST3Gal1

```
a-m, q-u (independently selected) = 0 or 1;

p = 1; n = 0;

v-y (independently selected) = 0 or 1;

R = linker-Urokinase.
```

/ FIG. 43.1

```
Isolated Urokinase.

a-d, i-m, q-u (independently selected) = 0 or 1;

e-h = 1; v-y = 0; n = 0;

Sia (independently selected) = Sia or SO<sub>4</sub>;

Gal (independently selected) = Gal or GalNAc;

GicNAc (independently selected) = GicNAc or GicNAc-Fuc.
```

sulfohydrolase
 CMP-SA-PEG, sialyltransferase

```
a-d, i-m, q-u (independently selected) = 0 or 1;
n = 0; e-h = 1; Sia = Sia;
Gal (independently selected) = Gal or GalNAc;
GlcNAc (independently selected) = GlcNAc or GlcNAc-Fuc.
v-y (independently selected) = 0 or 1;
R = PEG.
```

FIG. 43K

Isolated Urokinase.

a-d, i-m, q-u (independently selected) = 0 or 1;

e-h = 1; n = 0; v-y = 0;

Sia (independently selected) = Sia or SO₄;

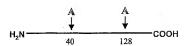
Gal (independently selected) = Gal or GalNAc;

GlcNAc (independently selected) = GlcNAc or GlcNAc-Fuc.

sulfohydrolase, hexosaminidase
 UDP-Gal-PEG, galactosyltransferase

a-d, i, q-u (independently selected) = 0 or 1; e-h = 1; j-n = 0; Gal (independently selected) = Gal; GleNAc (independently selected) = GleNAc or GleNAc-Fuc; v-y (independently selected) = 0 or 1; R = PEG.

FIG. 43L



$$A = \begin{array}{c} \text{(Fuc)}_{i_{j}} \\ \text{GlcNAc-GlcNAc-Man} \\ \text{Man} \\ \text{[[GlcNAc-(Gal)_{g}]_{g^{-}}(Sia)_{j} - (R)_{w})}_{t_{j}} \\ \text{[[GlcNAc-(Gal)_{g}]_{g^{-}}(Sia)_{l} - (R)_{w})}_{t_{j}} \\ \text{[[GlcNAc-(Gal)_{g}]_{g^{-}}(Sia)_{m^{-}}(R)_{y})}_{t_{j}} \\ \text{[[GlcNAc-(Gal)_{g}]_{g^{-}}(Sia)_{m^{-}}(R)_{y}}_{t_{j}} \\ \text{[[GlcNAc-(Gal)_{g}]_{g^{-}}(Sia)_{m^{-}}(R)_{y}}_{t_{j}} \\ \text{[[GlcNAc-(Gal)_{g}]_{g^{-}}(R)_{y}}_{t_{j}} \\ \text{[[GlcNAc-(Ga$$

a-d, i, q-u (independently selected) = 0 or 1. e-h (independently selected) = 0 to 6. j-m (independently selected) = 0 to 100. v-y = 0; R = polymer, glycoconjugate.

FIG. 44A

```
CHO, BHK, 293 cells, Vero expressed DNase I. a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; \mathbf{v}-\mathbf{y} = 0.
```

- Sialidase
- CMP-SA-PEG (16 mol eq), ST3Gal3

```
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1;
v-y (independently selected) = 1,
when j-m (independently selected) is 1;
R = PEG.
```

FIG. 44B

```
CHO, BHK, 293 cells, Vero expressed DNase I. a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y = 0.
```

- 1. Sialidase
- 2. CMP-SA-PEG (1.2 mol eq), ST3Gal3
- 3. CMP-SA (16 mol eq), ST3Gal3

```
a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y (independently selected) = 0 or 1; R = PEG.
```

FIG. 44C

```
CHO, BHK, 293 cells, Vero expressed DNase I. a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y = 0.
```

```
1. Sialidase
2. CMP-SA-PEG (16 mol eq), ST3Gal3
3. CMP-SA, ST3Gal3
```

```
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y (independently selected) = 0 or 1;
R = PEG.
```

FIG. 44D

```
CHO, BHK, 293 cells, Vero expressed DNase I. a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y = 0.
```

```
1. CMP-SA-levulinate, ST3Gal3, buffer, salt

▼ 2. H₄N}-PEG
```

```
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y (independently selected) = 0 or 1;
R = PEG.
```

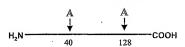
FIG. 44E

```
CHO, BHK, 293 cells, Vero expressed DNase I. a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y = 0.
```

```
1. CMP-SA, α2,8-ST
```

```
a-d, i, q-u (independently selected) = 0 or 1;
e-h = 1;
j-m (independently selected) = 0-20;
v-y (independently selected) = 0.
```

FIG. 44F



$$A^{\bullet} \underbrace{ \begin{bmatrix} \left[\operatorname{GloNAc-(Gal)_{a}}_{a}\right]_{e}^{-} \left(\operatorname{Sia}\right)_{j}^{-} \left(\operatorname{R}\right)_{v} \right]_{r}^{}}_{\left[\left[\operatorname{GloNAc-(Gal)_{a}}\right]_{e}^{-} \left(\operatorname{Sia}\right)_{k}^{-} \left(\operatorname{R}\right)_{w} \right]_{q}^{}} \\ \underbrace{ \begin{bmatrix} \left[\operatorname{GloNAc-(Gal)_{a}}\right]_{r}^{-} \left(\operatorname{Sia}\right)_{r}^{-} \left(\operatorname{R}\right)_{w} \right]_{q}^{}}_{\left[\left[\operatorname{GloNAc-(Gal)_{a}}\right]_{h}^{-} \left(\operatorname{Sia}\right)_{h}^{-} \left(\operatorname{R}\right)_{y} \right]_{q}^{}} \\ \underbrace{ \begin{bmatrix} \left[\operatorname{GloNAc-(Gal)_{a}}\right]_{h}^{-} \left(\operatorname{Sia}\right)_{h}^{-} \left(\operatorname{R}\right)_{y} \right]_{q}^{}}_{q} \\ \underbrace{ \begin{bmatrix} \left[\operatorname{GloNAc-(Gal)_{a}}\right]_{h}^{-} \left(\operatorname{Sia}\right)_{h}^{-} \left(\operatorname{R}\right)_{y} \right]_{q}^{}}_{q} \\ \underbrace{ \begin{bmatrix} \left[\operatorname{GloNAc-(Gal)_{a}}\right]_{h}^{-} \left(\operatorname{Sia}\right)_{h}^{-} \left(\operatorname{R}\right)_{y} \right]_{q}^{}}_{q} \\ \underbrace{ \begin{bmatrix} \left[\operatorname{GloNAc-(Gal)_{a}}\right]_{h}^{-} \left(\operatorname{Sia}\right)_{h}^{-} \left(\operatorname{R}\right)_{y} \right]_{q}^{}}_{q} \\ \underbrace{ \begin{bmatrix} \left[\operatorname{GloNAc-(Gal)_{a}}\right]_{h}^{-} \left(\operatorname{Sia}\right)_{h}^{-} \left(\operatorname{R}\right)_{y} \right]_{q}^{}}_{q} \\ \underbrace{ \begin{bmatrix} \left[\operatorname{GloNAc-(Gal)_{a}}\right]_{h}^{-} \left(\operatorname{Sia}\right)_{h}^{-} \left(\operatorname{R}\right)_{y} \right]_{q}^{}}_{q} \\ \underbrace{ \begin{bmatrix} \left[\operatorname{GloNAc-(Gal)_{a}}\right]_{h}^{-} \left(\operatorname{Sia}\right)_{h}^{-} \left(\operatorname{R}\right)_{y} \right]_{q}^{}}_{q} \\ \underbrace{ \begin{bmatrix} \left[\operatorname{GloNAc-(Gal)_{a}}\right]_{h}^{-} \left(\operatorname{Sia}\right)_{h}^{-} \left(\operatorname{R}\right)_{y} \right]_{q}^{}}_{q} \\ \underbrace{ \begin{bmatrix} \left[\operatorname{GloNAc-(Gal)_{a}}\right]_{h}^{-} \left(\operatorname{Sia}\right)_{h}^{-} \left(\operatorname{R}\right)_{y} \right]_{q}^{}}_{q} \\ \underbrace{ \begin{bmatrix} \left[\operatorname{GloNAc-(Gal)_{a}}\right]_{h}^{-} \left(\operatorname{Sia}\right)_{h}^{-} \left(\operatorname{R}\right)_{h}^{-} \left(\operatorname{R}\right)_{h}^{-} \left(\operatorname{R}\right)_{h}^{-} \left(\operatorname{R}\right)_{h}^{-} \left(\operatorname{R}\right)_{h}^$$

a-d, i, n, p-n (independently selected) = 0 or 1.
e-h (independently selected) = 0 to 6.
j-m (independently selected) = 0 to 100.
v-y = 0;
R = modifying group, mannose, oligo-mannose;
R' = H, glycosyl residue, modifying group,
glycoconjugate.

FIG. 44G

```
Insect cell expressed DNase I. a-d, f, h, j-n, s, u, v-y = 0; e, g, i, q, r, t (independently selected) = 0 or 1.
```

```
1. GNT's 1,2,4,5, UDP-GlcNAc
2. Galactosyltransferase, UDP-Gal-PEG
```

```
a-i, q-u (independently selected) = 0 or 1; j-n = 0; v-y (independently selected) = 1, when e-h (independently selected) is 1; R = PEG.
```

FIG. 44H

```
Yeast expressed DNase I.
a-n = 0;
q-y (independently selected) = 0 to 1;
p = 1; R (branched or linear) = Man, oligomannose.
```

```
    Endoglycanase
    Galactosyltransferase, UDP-Gal
    CMP-SA-PEG, ST3Gal3
```

```
a-n, p-y=0; n (independently selected) = 0 or 1; R'=-Gal-Sia-PEG.
```

FIG. 441

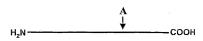
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CHO, BHK, 293 cells, Vero expressed DNase I. a-d, i-m, q-u (independently selected) = 0 or 1; e-h=1; n, v-y=0.

- CMP-SA-linker-SA-CMP, ST3Gal3
 ST3Gal1, desialylated alpha-1 Proteinase inhibitor.
- 3. CMP-SA, ST3Gal3, ST3Gal1 a-m, q-u (independently selected) = 0 or 1;
- p = 1; n = 0;
- v-y (independently selected) = 0 or 1;
- R = linker- alpha-1-Proteinase inhibitor.

FIG. 44J



$$(Fuc)_{i} \\ A \leftarrow GlcNAc\text{-}GlcNAc\text{-}Man \\ (R')_{n} \\ (RC)_{n} \\ (RGlcNAc\text{-}Gal)_{a}l_{r} - (Sia)_{s} - (R)_{w} \\ (RGlcNAc\text{-}Gal)_{a}l_{r} - (Sia)_{s} - (R)_{w} \\ (RGlcNAc\text{-}Gal)_{a}l_{r} - (Sia)_{r} - (R)_{s} \\ (RGlcNAc\text{-}Gal)_{a}l_{r} - (Sia)_{m} - (R)_{y} \\ (RGlcNAc\text{-}Gal)_{a}l_{r} - (RGlCNAc\text{-}Gal)_{$$

a-d, i, r-u (independently selected) = 0 or 1.
e-h (independently selected) = 0 to 4.
'
j-m (independently selected) = 0 or 1.
n, v-y = 0; z = 0 or 1;
R = modifying group, mannose, oligo-mannose;
R' = H, glycosyl residue, modifying group,
glycoconjugate.

FIG. 45A

```
CHO, BHK, 293 cells, Vero expressed Insulin.
a-m, r-u (independently selected) = 0 or 1;
n = 0; v-y = 0; z = 1.
```

```
    Sialidase
    CMP-SA-PEG, ST3Gal3
```

```
a-m, r-u (independently selected) = 0 or 1;
v-y (independently selected) = 1,
when j-m (independently selected) is 1;
n = 0; R = PEG; z = 1.
```

FIG. 45B

```
Insect cell expressed Insulin.

a-h, j-n, s-y = 0;

i, r (independently selected) = 0 or 1; z = 1.

1. GNT's 1&2, UDP-GlcNAc-PEG

a-d, f, h, j-n, s, u, w, y = 0;
e, g, i, r, t, v, x (independently selected) = 0 or 1;
v, x (independently selected) = 1,
when e, g (independently selected) is 1;
z = 1; R = PEG.
```

FIG. 45C

Yeast expressed Insulin.

a-n=0; r-y (independently selected) = 0 to 1;

z = 1;

R (branched or linear) = Man, oligomannose or polysaccharide.

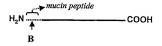
1. Endo-H

2. Galactosyltransferase, UDP-Gal-PEG

a-m, r-z= 0; n = 1; R' = -Gal-PEG.

FIG. 45D





$$\mathbf{B} \leftarrow \begin{bmatrix} (\operatorname{Sia})_{b} \\ -(\operatorname{GalNAc-(Gal)}_{a} - (\operatorname{Sia})_{c} - (\operatorname{R})_{d} \end{bmatrix}_{c}$$

a-c, e (independently selected) = 0 or 1; d = 0; R = polymer

FIG. 45E

CHO, BHK, 293 cells, Vero expressed insulinmucin fusion protein.

a-c, e (independently selected) = 0 or 1; d = 0

Sialidase
 CMP-SA-PEG, ST3Gal1

a-d, e (independently selected) = 0 or 1; R = PEG.

FIG. 45F

Insect cell expressed Insulin-mucin fusion protein. a, e (independently selected) = 0 or 1; b, c, d = 0.

1. Galactosyltransferase, UDP-Gal-PEG

a, d, e (independently selected) = 0 or 1; b, c = 0; R = PEG.

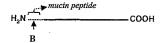
FIG. 45G

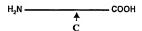
E. coli expressed Insulin-mucin fusion protein. a-e=0.

- GalNAc Transferase, UDP-GalNAc
 CMP-SA-PEG, sialyltransferase
- ▼ ...
- c, d, e (independently selected) = 0 or 1; a, b = 0; R = PEG.

FIG. 45H







$$\mathbf{B} \leftarrow \begin{bmatrix} (\mathrm{Sia})_b \\ -\mathrm{GalNAc-(Gal)_a-(Sia)_c-(R)_d} \end{bmatrix}_c$$

$$C \leftarrow (R')_n$$

a-c, e (independently selected) = 0 or 1; d=0; R= modifying group, mannose, oligo-mannose.

FIG. 451

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E. coli expressed Insulin-mucin fusion protein. a-e, n=0.

GalNAc Transferase,
 UDP-GalNAc-PEG

d, e (independently selected) = 0 or 1; a-c, n = 0; R = PEG.

FIG. 45J

E. coli expressed Insulin-mucin fusion protein. a-e, n=0.

- GalNAc Transferase,
 UDP-GalNAc-linker-SA-CMP
 - 2. ST3Gal3, asialo-transferrin
 - 3. CMP-SA, ST3Gal3

d, e (independently selected) = 0 or 1; a-c, n = 0; R = linker-transferrin.

FIG. 45K

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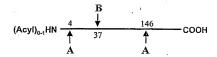
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E. coli expressed Insulin (N)—no mucin peptide. a-e, n=0.

- 1. NHS-CO-linker-SA-CMP
- 2. ST3Gal3, asialo-transferrin
- 3. CMP-SA, ST3Gal3

a-e = 0; n = 1; R' = linker-transferrin.

FIG. 45L



$$A \leftarrow \begin{bmatrix} (\operatorname{Fuc})_i & & & & & \\ (\operatorname{Fuc})_i & & & \\ (\operatorname{Fuc})_i & & & & \\ (\operatorname{Fuc})_i & & & \\ (\operatorname{Fuc$$

a-d, i, n-u, aa (independently selected) = 0 or 1. e-h (independently selected) = 0 to 6. j-m (independently selected) = 0 to 100. v-y = 0; R = polymer, glycoconjugate.

FIG. 46A

CHO, BHK, 293 cells, Vero expressed M-antigen. a-d, i-m, o-u, aa (independently selected) = 0 or 1; n, e-h = 1; v-z=0.

Sialidase
 CMP-SA-linker-lipid-A,
 ST3Gal3

a-d, i-m, q-u, aa (independently selected) = 0 or 1; o, p, z = 0; n, e-h = 1; v-y (independently selected) = 1, when j-m (independently selected) is 1; R = linker-lipid-A.

FIG. 46B

CHO, BHK, 293 cells, Vero expressed M-antigen. a-d, i-m, o-u, as (independently selected) = 0 or 1; h, e-h = 1; v-z=0.

- sialidase
 CMP-SA-linker-tetanus toxin, ST3Gall
 CMP-SA, ST3Gal3
- a-d, i-m, p-u, z, as (independently selected) = 0 or 1; o, v-y = 0; n, e-h = 1; R = tetanus toxin.

FIG. 46C

```
NSO expressed M-antigen.
a-d, i-n, o-u, aa (independently selected) = 0 or 1;
e-h = 1; v-z = 0;
Sia (independently selected) = Sia or Gal.
```

```
    α-galactosidase
    CMP-SA, ST3Gal3
    CMP-SA-KLH, ST3Gal1
```

```
a-d, i-n, p-u, z, as (independently selected) = 0 or 1;
e-h = 1; o, v-y = 0;
z = 1, when p = 1;
R = KLH.
```

FIG. 46D

```
Yeast expressed M-antigen.
a-p, z = 0; q-y, aa (independently selected) = 0 to 1;
R (branched or linear) = Man, oligomannose;
GalNAc = Man.
```

```
1. α1,2-mannosidase
2. GNT 1,
UDP-GlcNAc-linker-diphtheria toxin.
```

```
e, q, l, m, r, t, u, v, aa (independently selected) =0 or 1;
a-d, f-h, j, k, n-p, s, w-z = 0;
Sia = Man; R = linker-diphtheria toxin.
```

FIG. 46E

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CHO, BHK, 293 cells, Vero expressed M-antigen. a-d, i-m, o-u, aa (independently selected) = 0 or 1; n, e-h = 1; v-z=0.

1. CMP-SA-levulinate, ST3Gal3, 2. H₄N₂-linker-DNA

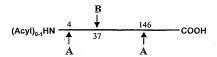
a-d, i-m, o-y, as (independently selected) = 0 or 1; z = 0; n, e-h = 1; R = linker-DNA.

FIG. 46F

CHO, BHK, 293 cells, Vero expressed M-antigen. a-d, i-n, o-u, as (independently selected) = 0 or 1; e-h = 1; v-z = 0. 1. CMP-SA, poly- α 2,8-ST

a-d, i, n-u, aa (independently selected) = 0 or 1; e-h = 1; j-m (independently selected) = 0-100; v-z (independently selected) = 0.

FIG. 46G



$$\begin{array}{c} A \leftarrow \begin{pmatrix} (\operatorname{Fuc})_i \\ -\operatorname{GlcNAc-GlcNAc-Man} \\ | R')_{cc} \end{pmatrix} \\ \begin{array}{c} \operatorname{Man} \left([\operatorname{GlcNAc-(Gal)_b}]_c - (\operatorname{Sia})_i - (R)_v \\ | [\operatorname{GlcNAc-(Gal)_b}]_r - (\operatorname{Sia})_k - (R)_w \\ | \\ \operatorname{Man} \left([\operatorname{GlcNAc-(Gal)_b}]_s - (\operatorname{Sia})_i - (R)_x \\ | \\ ([\operatorname{GlcNAc-(Gal)_d}]_h - (\operatorname{Sia})_h - (R)_y \\ | \\ \end{array} \right)_{bb} \end{array}$$

a-d, i, n, q-u, aa, bb, (independently selected) = 0 or 1. e-h (independently selected) = 0 to 6. j-p (independently selected) = 0 to 100. Cc, v-y = 0; R = modifying group, mannose, oligo-mannose. R'=H, glycosyl residue, modifying group, glycoconjugate.

FIG. 46H

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```
Insect cell expressed M-antigen. a-d, f, h, j-m, o, p, s, u, v-z, cc = 0; bb = 1; e, g, i, n, q, r, t, aa (independently selected) = 0 or 1.
```

l. GNT-2, UDP-GlcNAc-linker-Neisseria protein

```
a, c, e, g, i, n, q, r, t, v, x, aa (independently selected) = 0 or 1; b, d, f, h, j-p, s, u, w, y, z, cc = 0; bb = 1; R = -linker-Neisseria protein.
```

FIG. 46!

```
Yeast expressed M-antigen.
a-p, z, cc = 0;
q-y, aa (independently selected) = 0 to 1;
bb = 1; R (branched or linear) = Man, oligomannose;
GalNAc = Man.
```

```
    1. Endoglycanase
    2. Galactosyltransferase,
    UDP-Gal-linker-Neisseria protein
```

```
a-p, r-z, bb = 0;
q, aa, cc (independently selected) = 0 or 1;
R' = -Gal-linker-Neisseria protein.
```

FIG. 46J

Yeast expressed M-antigen.

a-p, z, cc = 0;

q-y, as (independently selected) = 0 to 1; bb = 1;

R (branched or linear) = Man, oligomannose;

GalNAc = Man.

- 1. mannosidases
- 2. GNT 1 & 2, UDP-GlcNAc
 3. UDP-Gal, Galactosyltransferase,
 4. CMP-SA, sialyltransferase

a, c, e, g, j, l, q, r, t, aa (independently selected) = 0 or 1; b, d, f, h, k, m-p, s, u-z, cc = 0; bb = 1.

FIG. 46K



$$(Fuc)_{i} \\ A \leftarrow GlcNAc \\ -GlcNAc \\$$

a-d, i, r-u (independently selected) = 0 or 1.
e-h (independently selected) = 0 to 4.
j-m (independently selected) = 0 or 1.
n, v-y = 0; z = 0 or 1;
R - modifying group, mannose, oligo-mannose;
R' = H, glycosyl residue, modifying group,
glycoconjugate.

FIG. 47A

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CHO, BHK, 293 cells, Vero expressed Growth Hormone.

a-m, r-u (independently selected) = 0 or 1; n = 0; v-y = 0; z = 1.

Sialidase
 CMP-SA-PEG, ST3Gal3

a-m, r-u (independently selected) = 0 or 1; v-y (independently selected) = 1, when j-m (independently selected) is 1; n = 0; R = PEG; z = 1.

FIG. 47B

$$\label{eq:continuous} \begin{split} & \text{Insect cell expressed growth hormone.} \\ & \text{a-h, j-n, s-y} = 0; \\ & \text{i, r (independently selected)} = 0 \text{ or l; } z = 1. \end{split}$$

1. GNT's 1&2, UDP-GlcNAc-PEG

a-d, f, h, j-n, s, u, w, y = 0; e, g, i, r, t, v, x (independently selected)= 0 or 1; v, x (independently selected) = 1, when e, g (independently selected) is 1; z = 1; R = PEG.

FIG. 47C

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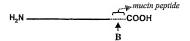
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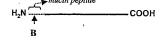
Yeast expressed growth hormone. a-n = 0; r-y (independently selected) = 0 to 1; z = 1; R (branched or linear) = Man, oligomannose or polysaccharide.

> l. Endo-H 2. Galactosyltransferase, UDP-Gal-PEG

a-m, r-z= 0; n = 1; R' = -Gal-PEG.

FIG. 47D





$$\mathbf{B} \leftarrow \begin{bmatrix} (\mathrm{Sia})_b \\ -\mathrm{GalNAc-(Gal)_a-(Sia)_c - (R)_d} \end{bmatrix}$$

a-c, e (independently selected) = 0 or 1; d = 0:

R = modifying group, mannose, oligomannose.

FIG. 47E

CHO, BHK, 293 cells, Vero expressed growth hormone-mucin fusion protein.

a-c, e (independently selected) = 0 or 1; d = 0

- Sialidase
 - 2. CMP-SA-PEG, ST3Gal1

a-d, e (independently selected) = 0 or 1; R = PEG.

FIG. 47F

Insect cell expressed Growth Hormone-mucin fusion protein.

a, e (independently selected) = 0 or 1; b, c, d = 0.

Galactosyltransferase, UDP-Gal-PEG

a, d, e (independently selected) = 0 or 1; b, c = 0; R = PEG.

FIG. 47G

E. coli expressed growth hormone-mucin fusion protein.

a-e = 0.

GalNAc Transferase, UDP-GalNAc
 CMP-SA-PEG, sialyltransferase

c, d, e (independently selected) = 0 or 1; a, b = 0; R = PEG.

FIG. 47H

E. coli expressed growth hormone-mucin fusion protein. a-e, n = 0.

GalNAc Transferase,
 UDP-GalNAc-PEG

d, e (independently selected) = 0 or 1; a-c, n = 0; R = PEG.

FIG. 471

E. coli expressed growth hormone-mucin fusion protein.

a-e, n=0.

1. GalNAc Transferase,
UDP-GalNAc-linker-SA-CMP
2. ST3Gal3, asialo-transferrin
3. CMP-SA. ST3Gal3

d, e (independently selected) = 0 or 1; a-c, n = 0; R = linker-transferrin.

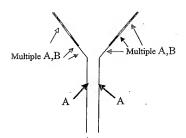
FIG. 47J

E. coli expressed growth hormone
(N)—no mucin peptide.
a-e, n = 0.

NHS-CO-linker-SA-CMP
 ST3Gal3, asialo-transferrin
 CMP-SA, ST3Gal3

a-e=0; n=1; R'=linker-transferrin.

FIG. 47K



a-d, i-m, q-u, w, z, nn, ww, zz (independently selected) = 0 or 1. e-h (independently selected) = 0 to 4.

n, v-y = 0;

R = modifying group, mannose, oligo-mannose;

R' = H, glycosyl residue, modifying group, glycoconjugate.

FIG. 48A

CHO, BHK, 293 cells, Vero or transgenic animals expressed TNF Receptor IgG Fusion. a-m, o-u, as (independently selected) = 0 or 1; n=1; v-z=0.

```
    CMP-SA, ST3Gall
    galactosyltransferase, UPD-Gal
    CMP-SA-PEG, ST3Gal3
```

```
a-m, o-u, v-y, aa (independently selected) = 0 or 1; n = 1; z = 0; R = PEG.
```

FIG. 48B

```
CHO, BHK, 293 cells, Vero expressed TNF Receptor IgG Fusion. a-m, o-u, aa (independently selected) = 0 or 1; n=1; v-z=0.
```

```
1. sialidase

✓ 2. CMP-SA-PEG, ST3Gal1
```

```
a-i, p-u, z, aa (independently selected) = 0 or 1;

n = 1; o, j-m, v-y = 0; R = PEG.
```

FIG. 48C

```
CHO, BHK, 293 cells, Vero expressed
TNF Receptor IgG Fusion.
a-m, o-u, aa (independently selected) = 0 or 1;
n = 1; v-z = 0.
```

1. galactosyltransferase, UPD-Gal-PEG

```
a-m, o-u, v-y; aa (independently selected) = 0 or 1; n = 1; z = 0; R = PEG.
```

FIG. 48D

```
CHO; BHK, 293 cells, Vero or transgenic animals expressed TMF Receptor IgG Fusion. a-m, o-u, as (independently selected) = 0 or 1; n = 1; v - z = 0.
```

```
    1. CMP-SA, ST3Gall
    2. galactosyltransferase, UPD-Gal-PEG
```

```
a-m, o-u, v-y, aa (independently selected) = 0 or 1;

n = 1; z = 0; R = PEG.
```

FIG. 48E

CHO, BHK, 293 cells, Vero or transgenic animals expressed TNF Receptor IgG Fusion. a-m, o-u, as (independently selected) = 0 or 1; n=1; v-z=0.

```
1. CMP-SA-levulinate, ST3Gal1

▼ 2. H<sub>a</sub>N<sub>3</sub>-PEG
```

```
a-m, o-u, v-y, aa (independently selected) = 0 or 1; n=1; z=0; R=PEG.
```

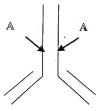
FIG. 48F

```
CHO, BHK, 293 cells, Vero expressed
TNF Receptor IgG Fusion.
a-m, o-u, aa (independently selected) = 0 or 1;
n = 1; v-z = 0.
```

```
1. CMP-SA-PEG, \alpha2,8-ST
```

```
a-i, o, q-u, v-z, as (independently selected) = 0 or 1; n = 1; j-m, p (independently selected) = 0 to 2; v-z (independently selected) = 1, when j-m, p (independently selected) is 2; R = PEG.
```

FIG. 48G



$$A \leftarrow \begin{bmatrix} \text{Fuc}_{i} \\ \text{GicNAc-Gal}_{al_{a}} \\$$

a-d, i, l, q-u (independently selected) = 0 or 1.

e-h (independently selected) = 0 to 4.

j-k (independently selected) = 0 or 1.

M = 0 to 20.

n, v-y = 0; z = 0 or 1;

R = polymer, toxin, radioisotope-complex, drug, mannose, oligo-mannose.

R' = H, glycosyl residue, modifying group, glycoconjugate.

FIG. 49A

```
CHO, BHK, 293 cells, Vero expressed Herceptin. a, c, i (independently selected) = 0 or 1; e, g, r, t = 1; b, d, f, h, j-m, n, s, u-y = 0; q, z = 1.
```

galactosyltransferase, UPD-Gal
 CMP-SA-toxin, ST3Gal3

```
a, c, i, j, l (independently selected) = 0 or 1;
e, g, r, t = 1; R = toxin;
f, h, k, m, n, s, u - y = 0; q, z = 1;
v-y (independently selected) = 51,
when j, l (independently selected) is 1.
```

FIG. 49B

```
CHO, BHK, 293 cells, Vero or fungal expressed Herceptin.

a, c, i (independently selected) = 0 or 1;

e, g, r, t = 1; b, d, f, h, j-m, n, s, u-y = 0;

q, z = 1.
```

 galactosyltransferase, UPD-Gal-Toxin

```
a, c, i (independently selected) = 0 or 1;
e, g, r, t=1; f, h, j-m, n, s, u-y = 0;
q, z=1; v-y (independently selected) = 1,
when a, c (independently selected) is 1;
R = toxin.
```

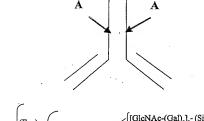
FIG. 49C

Fungi expressed Herceptin. e, g, i, r, t (independently selected) = 0 or 1; a-d, f, h, j-m, n, s, u-y = 0; q, z = 1.

- 1. Endo-H
- 2. Galactosyltransferase, UDP-Gal
- ▼ 3.. CMP-SA-radioisotope complex, ST3Gal3

a-m, r-z=0; q, n = 1; R'=-Gal-Sia-radioisotope complex.

FIG. 49D



$$A \leftarrow \begin{array}{c} \text{(Fuc)}_{i} \\ \text{(GlcNAc-(Gal)}_{a}l_{a^{-}}(\text{Sia)}_{i}^{-}(R)_{v} \\ \text{(GlcNAc-(Gal)}_{b}l_{r^{-}}(\text{Sia)}_{k^{-}}(R)_{w} \\ \text{(GlcNAc-Man } \\ \text{(GlcNAc-(Gal)}_{p} \\ \text{(GlcNAc-(Gal)}_{d}l_{h^{-}}(\text{Sia})_{m^{-}}(R)_{y} \\ \text{(GlcNAc-(Gal)}_{d}l_{h^{-}}(\text{Sia})_{m^{-}}(R)_{y} \\ \text{(GlcNAc-(Gal)}_{d}l_{h^{-}}(\text{Sia})_{m^{-}}(R)_{y} \\ \text{(GlcNAc-(Gal)}_{d}l_{h^{-}}(\text{Sia})_{m^{-}}(R)_{y} \\ \text{(GlcNAc-(Gal)}_{d}l_{h^{-}}(R)_{y} \\ \text{(GlcNAc-($$

a-d, i, p-u, (independently selected) = 0 or 1.

e-h (independently selected) = 0 to 4.

j-m (independently selected) = 0 or 1.

y = 0; z = 0 or 1;

R = polymer, toxin, radioisotope-complex, drug, mannose, oligo-mannose.

R' = H, glycosyl residue, modifying group, glycoconjugate.

FIG. 50A

```
CHO, BHK, 293 cells, Vero expressed Synagis. a, c, i (independently selected) = 0 or 1; e, g, r, t = 1; b, d, f, h, j-m, n, s, u-y = 0; q, z = 1.
```

galactosyltransferase, UPD-Gal
 CMP-SA-PEG, ST3Gal3

```
a, c, i, j, w, (independently selected) = 0 or 1;
e, g, r, t = 1; f, h, k, m, n, s, u-y = 0;
q, z = 1; v-y (independently selected) = 1,
when j, l (independently selected) is 1;
R = PEG.
```

FIG. 50B

```
CHO, BHK, 293 cells, Vero or fingal expressed Synagis.

a, c, i (independently selected) = 0 or 1;

e, g, f, t = 1; b, d, f, h, j-m, n, s, u-y = 0;

q, z = 1.
```

 galactosyltransferase, UPD-Gal-PEG

```
a, c, i, w (independently selected) = 0 or 1;
e, g, r, t = 1; f, h, j-m, n, s, u-y = 0;
q, z = 1; v-y (independently selected) = 1,
when a, c (independently selected) is 1;
R = PEG.
```

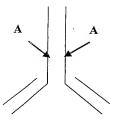
FIG. 50C

Fungi expressed Synagis. e, g, i, r, t (independently selected) = 0 or 1; a-d, f, h, j-m, n, s, u-y = 0; q, z = 1.

1. Endo-H
2. Galactosyltransferase, UDP-Gal
3.: CMP-SA-PEG, ST3Gal3

a-m, r-z=0; q, n = 1; R' = -Gal-Sia-PEG.

FIG. 50D



$$A \leftarrow \begin{bmatrix} (\operatorname{Fuc})_i \\ \operatorname{GlcNAc-\operatorname{Gal}}_b \end{bmatrix}_e - (\operatorname{Sia})_i - (\operatorname{R})_v \end{bmatrix}_r \\ \left[(\operatorname{GlcNAc-\operatorname{Gal}}_b)_i - (\operatorname{Sia})_i - (\operatorname{R})_v \end{bmatrix}_r \\ \left[(\operatorname{GlcNAc-\operatorname{Gal}}_b)_i - (\operatorname{Sia})_i - (\operatorname{R})_v \end{bmatrix}_r \right] \\ \left[(\operatorname{GlcNAc-\operatorname{Gal}}_b)_i - (\operatorname{Sia})_i - (\operatorname{R})_v \end{bmatrix}_r \\ \left[(\operatorname{GlcNAc-\operatorname{Gal}}_b)_i - (\operatorname{Sia})_i - (\operatorname{R})_v \end{bmatrix}_r \right] \\ \left[(\operatorname{GlcNAc-\operatorname{Gal}}_b)_i - (\operatorname{Sia})_i - (\operatorname{R})_v \end{bmatrix}_r \right] \\ \left[(\operatorname{GlcNAc-\operatorname{Gal}}_b)_i - (\operatorname{Sia})_i - (\operatorname{R})_v \end{bmatrix}_r \right] \\ \left[(\operatorname{GlcNAc-\operatorname{Gal}}_b)_i - (\operatorname{Sia})_i - (\operatorname{R})_v \end{bmatrix}_r \right]$$

a-d, i, q-u, w (independently selected) = 0 or 1.

e-h (independently selected) = 0 to 6.

j-m (independently selected) = 0 to 20.

n, v-y=0; z=0 or 1;

R = polymer, toxin, radioisotope-complex, drug, mannose, oligo-mannose.

R' = H, glycosyl residue, modifying group, glycoconjugate.

FIG. 51A

```
CHO, BHK, 293 cells, Vero expressed Remicade. a, c, i (independently selected) = 0 or 1; e, g, r, t = 1; b, d, f, h, j-m, n, s, u-y = 0; q, z = 1.
```

galactosyltransferase, UPD-Gal
 CMP-SA-PEG, ST3Gal3

```
\begin{split} &a,c,i,j,1 \text{ (independently selected)} = 0 \text{ or } 1;\\ &e,g,r,t=1; \ f,\ h,\ k,\ m,\ n,\ s,\ u-y=0;\\ &q,z=1;\ v-y \text{ (independently selected)} = 1,\\ &when\ j,1 \text{ (independently selected)} \text{ is } 1;\\ &R=PEG. \end{split}
```

FIG: 51B

```
CHO, BHK, 293 cells, Vero or fungal expressed Remicade. 
a, c, i (independently selected) = 0 or 1; 
e, g, r, t = 1; b, d, f, h, j-m, n, s, u-y=0; 
q, z=1.
```

 galactosyltransferase, UPD-Gal-PEG

```
a, c, i (independently selected) = 0 or 1;
e, g, r, t = 1; f, h, j-m, n, s, u-y = 0;
q, z = 1; v-y (independently selected) = 1,
when a, c (independently selected) is 1;
R = PEG.
```

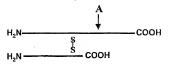
FIG. 51C

```
Fungi expressed Remicade.
e, g, i, r, t (independently selected) = 0 or 1;
a-d, f, h, j-m, n, s, u-y = 0; q, z = 1.
```

Eudo-H
 Galactosyltransferase, UDP-Gal
 CMP-SA-radioisotope complex, ST3Gal3

a-m, r-z=0; q, n = 1; R' = -Gal-Sia-radioisotope complex.

FIG. 51D



$$A \leftarrow \begin{bmatrix} (\operatorname{Fuc})_{i} & & & & \\ (\operatorname{GlcNAc-Gal})_{a}]_{c}^{*} \cdot (\operatorname{Sia})_{j}^{*} \cdot (\operatorname{R})_{v} \\ (\operatorname{GlcNAc-Gal})_{b}]_{r}^{*} \cdot (\operatorname{Sia})_{k}^{*} \cdot (\operatorname{R})_{v} \\ (\operatorname{R}')_{n} & & & \\ (\operatorname{R}')_{n} & & & \\ (\operatorname{GlcNAc-Gal})_{c}]_{g}^{*} \cdot (\operatorname{Sia})_{l}^{*} \cdot (\operatorname{R})_{y} \\ (\operatorname{GlcNAc-Gal})_{d}]_{h}^{*} \cdot (\operatorname{Sia})_{m}^{*} \cdot (\operatorname{R})_{y} \end{bmatrix}_{v}^{1}$$

a-d, i, q-u (independently selected) = 0 or 1. e-h (independently selected) = 0 to 4. j-m (independently selected) = 0 or 1. n, v-y = 0; z = 0 or 1; R = modifying group, mannose, oligo-mannose; R' = H, glycosyl residue, modifying group, glycoconjugate.

FIG. 52A

```
CHO, BHK, 293 cells, Vero expressed Reopro. a-m, r-u (independently selected) = 0 or 1; n=0; v-y=0; z=1.
```

```
    Sialidase
    CMP-SA-PEG, ST3Gal3
```

```
a-m, r-u (independently selected) = 0 or 1; v-y (independently selected) = 1, when j-m (independently selected) is 1; n=0; R=PEG; z=1.
```

FIG. 52B

```
Insect cell expressed Reopro.

a-h, j-n, s-y = 0; i, r (independently selected) = 0 or 1;

z = 1.

1. GNT's 1&2. UDP-GlcNAc-PEG
```

```
a-d, f, h, j-n, s, u, w, y = 0;
e, g, i, r, t, v, x (independently selected) = 0 or 1;
v, x (independently selected) = 1,
when e, g (independently selected) is 1;
z = 1; R = PBG.
```

FIG. 52C

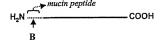
Yeast expressed Reopro.
a-n = 0; r-y (independently selected) = 0 to 1;
z = 1;
R (branched or linear) = Man, oligomannose or
polysaccharide.

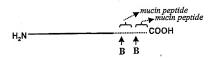
- I. Endo-H
- 2. Galactosyltransferase, UDP-Gal-PEG

a-m, r-z= 0; n = 1; R' = -Gal-PEG.

FIG. 52D







$$\mathbf{B} \leftarrow \begin{bmatrix} (\mathrm{Sia})_b \\ -\mathrm{GalNAc\text{-}}(\mathrm{Gal})_a - (\mathrm{Sia})_c - (\mathrm{R})_d \end{bmatrix}_c$$

a-c, e (independently selected) = 0 or 1; d = 0; R = polymer

FIG. 52E

CHO, BHK, 293 cells, Vero expressed Reopro-mucin fusion protein. a-c, e (independently selected) = 0 or 1; d=0

Sialidase
 CMP-SA-PEG, ST3Gal1

a-d, e (independently selected) = 0 or 1; R = PEG.

FIG. 52F

Insect cell expressed Reopro-mucin fusion protein. a, e (independently selected) = 0 or 1; b, c, d = 0.

1. Galactosyltransferase, UDP-Gal-PEG

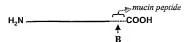
a, d, e (independently selected) = 0 or 1; b, c = 0; R = PEG.

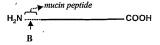
FIG. 52G

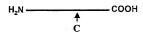
E. coli expressed Reopro-mucin fusion protein. a-e=0.

- 1. GalNAc Transferase, UDP-GalNAc
- 2. CMP-SA-PEG, sialyltransferase
- c, d, e (independently selected) = 0 or 1; a, b = 0; R = PEG.

FIG. 52H







$$\mathbf{B} \leftarrow \begin{pmatrix} (\operatorname{Sia})_b \\ \operatorname{GalNAc-(Gal)}_{a^-}(\operatorname{Sia})_c^- (\mathbb{R})_d \end{pmatrix}_e$$

 $\mathbb{C}^{\longleftarrow}(\mathbb{R}')_n$

a-c, e (independently selected) = 0 or 1; d = 0; R = polymer, linker.

FIG. 521

E. coli expressed Reopro-mucin fusion protein. a-e, n=0.

 GalNAc Transferase, UDP-GalNAc-PEG

d, e (independently selected) = 0 or 1; a-c, n = 0; R = PEG.

FIG. 52J

E. coli expressed Reopro-mucin fusion protein. a-e, n=0.

 GalNAc Transferase, UDP-GalNAc-linker-SA-CMP
 ST3Gal3, asialo-transferrin

3. CMP-SA, ST3Gal3

d, e (independently selected) = 0 or 1; a-c, n = 0; R = linker-transferrin.

FIG. 52K

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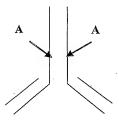
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E. coli expressed Reopro(N)—no mucin peptide. a-e, n=0.

- 1. NHS-CO-linker-SA-CMP
- 2. ST3Gal3, asialo-transferrin
- 3. CMP-SA, ST3Gal3

a-e = 0; n = 1; R' = linker-transferrin.

FIG. 52L



$$\mathbf{A} \leftarrow \begin{bmatrix} (\operatorname{Fuc})_{i} \\ \operatorname{GlcNAc-Gal})_{a,lc} \cdot (\operatorname{Sia})_{j} \cdot (\operatorname{R})_{v} \end{bmatrix}_{r} \\ \left[(\operatorname{GlcNAc-Gal})_{a,lc} \cdot (\operatorname{Sia})_{j} \cdot (\operatorname{R})_{v} \end{bmatrix}_{r} \\ \left[(\operatorname{GlcNAc-Gal})_{a,lc} \cdot (\operatorname{Sia})_{j} \cdot (\operatorname{R})_{w} \end{bmatrix}_{s} \\ \left[(\operatorname{GlcNAc-Gal})_{a,lc} \cdot (\operatorname{Sia})_{j} \cdot (\operatorname{R})_{s} \right]_{t} \\ \left[(\operatorname{GlcNAc-Gal})_{a,lc} \cdot (\operatorname{Sia})_{s} \cdot (\operatorname{Sia})_{s} \cdot (\operatorname{Sia})_{s} \right]_{t} \\ \left[(\operatorname{GlcNAc-Gal})_{a,lc} \cdot (\operatorname{Sia})_{s} \cdot (\operatorname{Sia})_{s} \cdot (\operatorname{Sia})_{s} \cdot (\operatorname{Sia})_{s} \right]_{t} \\ \left[(\operatorname{GlcNAc-Gal})_{a,lc} \cdot (\operatorname{Sia})_{s} \right]_{t} \\ \left[(\operatorname{Sia})$$

a-d, i, q-u (independently selected) = 0 or 1. e-h (independently selected) = 0 to 4. j-m (independently selected) = 0 or 1. n, v-y = 0; z = 0 or 1; R = polymer, toxin, radioisotope-complex, drug, glycoconjugate. R' = H, sugar, glycoconjugate.

FIG. 53A

```
CHO, BHK, 293 cells, Vero or transgenic animal expressed Rituxan. a, c, i (independently selected) = 0 or 1; e, g, t = 1; b, d, f, h, j-m, n, s, u-y = 0; q, z = 1.
```

```
    galactosyltransferase, UPD-Gal
    CMP-SA-toxin, ST3Gal3
```

```
a, c, i, j, 1 (independently selected) = 0 or 1;
e, g, r, t = 1;
f, h, k, m, n, s, u-y = 0; q, z = 1;
v-y (independently selected) = 1,
when j, I (independently selected) is 1;
R = toxin.
```

FIG. 53B

```
CHO, BHK, 293 cells, Vero or fungal expressed Rituxan. a, c, e, g, i, r, t (independently selected) = 0 or 1; b, d, f, h, j-m, n, s, u-y = 0; q, z = 1.
```

```
    galactosyltransferase,
UPD-Gal-drug
```

```
a, c, i (independently selected) = 0 or 1;
e, g, r, t = 1; f, h, j-m, n, s, u-y = 0; q, z = 1;
v-y (independently selected) = 1,
when a, c (independently selected) is 1;
R = toxin.
```

FIG. 53C

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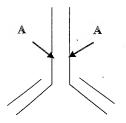
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Fungi expressed Rituxan. e, g, i, r, t (independently selected) = 0 or 1; a-d, f, h, j-m, n, s, u-y = 0; q, z = 1.

- 1. Endo-H
- 2. Galactosyltransferase, UDP-Gal
 3. CMP-SA-radioisotope complex, ST3Gal3

a-m, r-z=0; q, n=1; R' = -Gal-Sia-radioisotope complex.

FIG. 53D



$$\mathbf{A} \leftarrow \begin{bmatrix} (\operatorname{Fuc})_{i} & & & \\ (\operatorname{GlcNAc-Man})_{i} & & & \\ (\operatorname{GlcNAc-Man})_{i} & & & \\ (\operatorname{GlcNAc-Gal})_{a}_{i} & & & \\ (\operatorname{Glc$$

a-d, i, q-u (independently selected) = 0 or 1. e-h (independently selected) = 0 to 4. j-m (independently selected) = 0 or 1. n, v-y=0; z=0 or 1; R=polymer, toxin, radioisotope-complex, drug, glycoconjugate, mannose, oligo-mannose. <math>R'=H, glycosyl residue, modifying group, glycoconjugate.

FIG. 53E

```
CHO, BHK, 293 cells, Vero or transgenic animal expressed Rituxan. 
 a, c, i (independently selected) = 0 or 1; 
 e, g, r, t = 1; b, d, f, h, j-m, n, s, u-y = 0; 
 q, z = 1.
```

galactosyltransferase, UPD-Gal
 CMP-SA-PEG, ST3Gal3

```
a, c, i, j, 1 (independently selected) = 0 or 1;
e, g, r, t = 1; f, h, k, m, n, s, u-y = 0;
q, z = 1; v-y (independently selected) = 1,
when j, 1 (independently selected) is 1;
R = PEG.
```

FIG. 53F

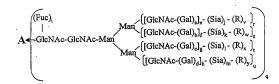
```
Fungi, yeast or CHO expressed Rituxan.
e, g, i, r, t, v, x (independently selected) = 0 or 1;
a-d, f, h, j-m, n, s, u, w, y = 0; q, z = 1;
R (independently selected) = mannose, oligomannose,
polymannose.
```

- 1. mannosidases (alpha and beta)
- GNT-I,II, UDP-GlcNAc
- ▼ 3. Galactosyltransferase, UDP-Gal-radioisotope

```
a-m, r-z=0; q, n = 1;
R' = -Gal-radioisotope complex.
```

FIG. 53G





a-d, i, q-u (independently selected) = 0 or 1. e-h (independently selected) = 0 to 6. j-m (independently selected) = 0 to 100. v-y = 0; R = mannose, polymer.

FIG. 54A

CHO, BHK, 293 cells, Vero or transgenic animal expressed AT III.
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y = 0.

 Sialidase
 CMP-SA-PEG (16 mol eq), ST3Gal3

a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y (independently selected) = 1, when j-m (independently selected) is 1; R = PEG.

FIG. 54B

CHO, BHK, 293 cells, Vero or transgenic animal expressed AT III. a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y = 0.

 Sialidase
 CMP-SA-PEG (1.2 mol eq), ST3Gal3
 CMP-SA (16 mol eq), ST3Gal3

a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y (independently selected) = 0 or 1; R = PEG.

FIG. 54C

```
NSO expressed AT III.
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h=1:
           v-y = 0;
Sia (independently selected) = Sia or Gal.
```

- 1. Sialidase and α-galactosidase 2. Galactosyltransferase, UDP-Gal
- ↓ 3. CMP-SA-PEG, ST3Gal3

```
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1;
v-y (independently selected) = 1,
  when j-m (independently selected) is 1;
R = PEG.
```

FIG. 54D

```
CHO, BHK, 293 cells, Vero or
  transgenic animal expressed AT III.
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h=1; v-y=0.
          1. Sialidase
          2. CMP-SA-PEG (16 mol eq),
             ST3Gal3
          3. CMP-SA, ST3Gal3
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1:
v-y (independently selected) = 0 or 1;
```

FIG. 54F

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CHO, BHK, 293 cells, Vero or transgenic animal expressed AT III. a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y = 0.

 CMP-SA-levulinate, ST3Gal3, buffer, salt
 H_aN₂-PEG

a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y (independently selected) = 0 or 1; R = PEG.

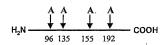
FIG. 54F

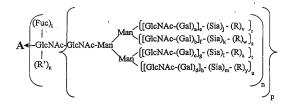
CHO, BHK, 293 cells, Vero expressed AT III. a-d, i-m, q-u (independently selected) = 0 or 1; e-h=1; v-y=0.

1. CMP-SA, poly-α2,8-ST

a-d, i, q-u (independently selected) = 0 or 1; e-h = 1; j-m (independently selected) = 0-20; v-y (independently selected) = 0.

FIG. 54G





a-d, i, p-u (independently selected) = 0 or 1. e-h (independently selected) = 0 to 6. j-m (independently selected) = 0 to 100. v-y = 0 to 100. R = polymer, linker, mamose. R' = H, sugar, glycoconjugate.

FIG. 54H

```
Insect, yeast or fungi cell expressed AT III.
a-d, f, h, j-n, s, u, v-y = 0;
e, g, i, q, r, t (independently selected) = 0 or 1;
p = 1.

1. GNT 1, UDP-GleNAc-PEG
```

```
\label{eq:continuous_selected} \begin{split} a, i, q, r, -u & (independently selected) = 0 \text{ or } 1; \\ b-g, j-n, s-u, w-y = 0; & p = 1; \\ v & (independently selected) = 1, \\ when a & (independently selected) \text{ is } 1; \\ R = PEG. \end{split}
```

FIG. 541

```
Yeast expressed AT III.

a-n = 0; q-y (independently selected) = 0 to 1;

p = 1;

R (branched or linear) = Man, oligomannose.
```

```
    1. Endoglycanase
    2. Galactosyltransferase, UDP-Gal
    3. CMP-SA-PEG, ST3Gal3
```

```
a-m, p-y = 0;
n (independently selected) = 0 or 1;
R' = -Gal-Sia-PEG.
```

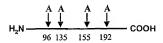
FIG. 54J

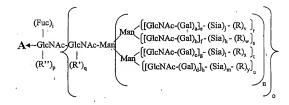
CHO, BHK, 293 cells, Vero expressed AT III. a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y=0.

- CMP-SA-linker-Gal-UDP, ST3Gal3
- Galactosyltransferase, transferrin treated with endoglycanase

a-m, q-u (independently selected) = 0 or 1; p = 1; n = 0; v-y (independently selected) = 0 or 1; R = linker-transferrin.

FIG. 54K





a-d, i, n-u (independently selected) = 0 or 1.

e-h (independently selected) = 0 to 4.

j-m (independently selected) = 0 to 20.

R = polymer.

R', R" (independently selected) = sugar, glycoconjugate.

FIG. 54L

```
Yeast expressed AT III.
a-h, i-m, p, q = 0;
R (independently selected) = mannose,
oligomannose, polymannose;
r-u, v-y (independently selected) = 0 or 1;
n, o = 1.
```

1. endoglycanase
 ▼ 2. Galactosyltransferase, UDP-Gal-PEG

```
a-h, i-o, q, r-u, v-y = 0; p = 1.
R" = Gal-PEG.
```

FIG. 54M

```
Plant expressed AT III.

a-d, f-h, j-m, p, s-u, v-y = 0;

c, i, q, r (independently selected) = 0 or 1;

n, o = 1; R' = xylose.
```

xylosidase

3. Galactosyl transferase, UDP-Gal-PEG

```
b-d, f-h, j-m, p, q, s-u, w-y = 0;
a, e, i, r (independently selected) = 0 or 1;
n, o = 1; R = PEG.
```

FIG. 54N

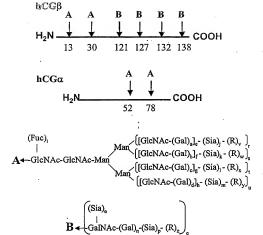
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CHO, BHK, 293 cells, Vero, transgenic animal expressed AT III.
a-h, i-o, r-u (independently selected) = 0 or 1;
p, q, v-y = 0.

1. CMP-SA-PEG, ST3Gal3

a-h, i-o, r-u (independently selected) = 0 or 1; p, q = 0; v-y (independently selected) = 0 or 1; R = PEG.

FIG. 540



a-d, i, n-u (independently selected) = 0 or 1. e-h (independently selected) = 0 to 4. j-m (independently selected) = 0 to 20. v-z = 0; R = polymer

FIG. 55A

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CHO, BHK, 293 cells, insect cell, Vero expressed hCG a-g, n, q = 1; h = 1 to 3; j-m, i, o, p (independently selected) = 0 or 1; r-u (independently selected) = 0 to1; v-z = 0

1. Sialidase
2. CMP-SA-PEG, ST3Gal3

a-g, n, q = 1; h = 1 to 3; i, o, p (independently selected) = 0 or 1; r-u (independently selected) = 0 or 1; j-m, v-y (independently selected) = 0 or 1; R = PEG; z = 0.

FIG. 55B

Insect cell, yeast, fungi expressed hCG a-d, f, h, j-m, o, p, s, u, v-z = 0; e, g, i, n, q, r, t (independently selected) = 0 or 1.

1. GNT's 1&2, UDP-GlcNAc
2. Galactosyltransferase, UDP-Gal
2. CMP-SA-PEG, ST3Gal3

 $\label{eq:bounds} \begin{array}{l} b,\,d,\,f,\,h,\,k,\,m,\,o,\,p,\,s,\,u,\,w,\,y,\,z=0;\\ a,\,c,\,e,\,g,\,i,\,n,\,q,\,r,\,t \ \ \mbox{(independently selected)}\\ =0\ \mbox{or}\ 1;\\ j,\,l,\,v,\,x \ \mbox{(independently selected)}=0\ \mbox{or}\ 1;\\ R=PEG. \end{array}$

FIG. 55C

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```
CHO, BHK, 293 cells, insect cell,
Vero expressed hCG
a-q, r-u (independently selected) = 0 or 1;
v-z = 0.
```

```
1. sialidase
2. CMP-SA, ST3Gal3
3. CMP-SA-PEG, ST3Gal1
```

```
a-h, i-o, q, r-u (independently selected) = 0 or 1;
v-y = 0; p, z = 0 or 1; R = PEG.
```

FIG. 55D

```
CHO, BHK, 293 cells, insect cell or
Vero expressed hCG
a-g, n, q = 1; h = 1 to 3;
j-m, i, o, p (independently selected) = 0 or 1;
r-u (independently selected) = 0 or 1; v-z = 0

1. CMP-SA-PÉG, ST3Gal3
```

```
a-g, n, q = 1; h = 1 to 3;
i, o, p (independently selected) = 0 or 1;
r-u (independently selected) = 0 to 1;
j-m, v-y (independently selected) = 0 or 1;
R = PEG; z = 0.
```

FIG. 55E

Insect cell, yeast or fungi expressed hCG a-d, f, h, j-m, o, p, s, u, v-z = 0; e, g, i, n, q, r, t (independently selected) = 0 or 1.

1. GNT's 1 and 2, UDP-GlcNAc-PEG

$$\label{eq:continuous_section} \begin{split} e,\,g,\,i,\,n,\,q,\,r,\,t,\,v,\,x \; (independently \; selected) \\ &= 0 \; or \; 1; \\ a\text{-d},\,f,\,b,\,j\text{-m},\,o,\,p,\,s,\,w,\,y,\,z = 0; \quad R = PEG. \end{split}$$

FIG. 55F

Insect cell, yeast or fungi expressed hCG a-d, f, h, j-m, o, p, s, u, v-z = 0; e, g, i, n, q, r, t (independently selected) = 0 or 1.

1. GNT-1, UDP-GlcNAc-PEG

 $\begin{array}{l} e,\,i,\,n,\,q,\,r,\,v\;(independently\;selected)=0\;\mathrm{or}\;1;\\ a\text{-}d,\,g,\,f,\,h,\,j\text{-}m,\,o,\,p,\,s,\,t,\,w\text{-}z=0; \end{array} \quad R=PEG.$

FIG. 55G

CHO, BHK, 293 cells, insect cell or Vero expressed hCG a-g, n, q = 1; h = 1 to 3; j-m, i, o, p (independently selected) = 0 or 1; r-u (independently selected) = 0 or 1; v-z = 0

CMP-SA-PEG, ST3Gal3

 $\begin{array}{lll} a\text{-g}, n, q = 1; & h = 1 \text{ to } 3;\\ i, o & (independently selected) = 0 \text{ or } 1;\\ r\text{-u} & (independently selected) = 0 \text{ to } 1;\\ j\text{-m}, p, z & (independently selected) = 0 \text{ or } 1;\\ R = PEG; & v\text{-y} = 0. \end{array}$

FIG. 55H

CHO, BHK, 293 cells, Vero expressed hCG a-g, n, q = 1; h = 1 to 3; j-m, i, o, p (independently selected) = 0 or 1; r-u (independently selected) = 0 or 1; v-z = 0

1. CMP-SA-PEG, a2,8-ST

a-g, n, q = 1; h = 1 to 3; i, o, p (independently selected) = 0 or 1; r-u (independently selected) = 0 to 1; j-m (independently selected) = 0 to 2; v-y (independently selected) = 1, when j-m (independently selected) is 2; R = PEG; z = 0.

FIG. 551

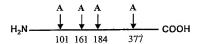
264/497

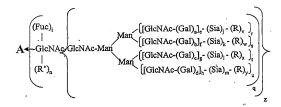
CHO, BHK, 293 cells, Vero expressed hCG
a-g, n, q = 1; h = 1 to 3;
j-m, i, o, p (independently selected) = 0 or 1;
r-u (independently selected) = 0 to 1; v-z = 0

1. 6.1.2. 51.3, poly 323,5 52

a-i, j-q, r-u, (independently selected) = 0 or 1; v-z (independently selected) = 0-100; R = Sia.

FIG. 55J





a-d, i, n, q^{-u} , z (independently selected) = 0 or 1. e-h (independently selected) = 0 to 6. j-m (independently selected) = 0 to 100. v-y = 0 to 100; R = mannose, mannose-6-phosphate and mannose, polymer.

FIG. 56A

CHO, BHK, 293 cells, insect cells, Vero expressed and secreted alpha-galactosidase
a-h, i-m, q-u (independently selected) = 0 or 1;
z = 1; n, v-y = 0; and when a-n = 0, then r-u (independently selected) = 0 or 1; v-y (independently selected) = 0-100;
R = mannose or mannose with mannose-6-phosphate.

1. Endo-H

2. Galactosyltransferase, UDP-Gal-PEG-transferrin

a-h, i-m, q-u (independently selected) = 0 or 1; n, v-y = 0; z = 1; and when z = 0 and q = 1, then n (independently selected) = 0 or 1; R' = Gal-PEG-transferrin.

FIG. 56B

CHO, BHK, 293 cells, Insect cells,

Vero expressed and secreted alpha-galactosidase a-h, i-m, q-u (independently selected) = 0 or 1; z=1; n, v-y = 0; and when a-n = 0, then r-u (independently selected) = 0 or 1; v-y (independently selected) = 0-100; R = mannose or mannose with mannose-6-phosphate.

Sialidase
 CMP-SA-linker-Mannose-6-phosphate
 ST3Gal3

a-h, i-m, q-u, v-y (independently selected) = 0 or 1_1^1 n = 0; z = 1; R = mannose-6-phosphate; and when a-n = 0, then r-u (independently selected) = 0 or 1; v-y (independently selected) = 0-100; R = mannose or mannose with mannose-6-phosphate.

FIG. 56C

NSO expressed alpha-galactosidase.

a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y=0;

Sia (independently selected) = Sia or Gal.

- 1. Sialidase and α-galactosidase
- 2. Galactosyltransferase, UDP-Gal
- CMP-SA-linker-mannose-6-phosphate sial vltransferase

a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y (independently selected) = 1, when j-m (independently selected) is 1; R = mannose-6 phosphate

FIG. 56D

CHO, BHK, 293 cells, Insect cells, Vero expressed and secreted alpha-galactosidase

a-h, i-m, q-u (independently selected) = 0 or 1; z = 1; n, v-y = 0; and when a-n = 0, then r-u (independently selected) = 0 or 1; v-y (independently selected) = 0-100; R = mannose or mannose with mannose-6-phosphate.

- 1. Sialidase
- 2. CMP-SA-PEG, sialyltransferase

a-h, i-m, q-u, v-y (independently selected) = 0 or 1; n = 0; z = 1; R = PEG; and when a-n = 0, then r-u (independently selected) = 0 or 1; v-y = 0-100; R = mannose or mannose with mannose-6-phosphate.

FIG. 56E

```
CHO, BHK, 293 cells, Insect cells, Vero, yeast, fungi expressed alpha-galactosidase.

a-i, vy = 0; q (independently selected) = 0 or 1; z = 1; r-u (independently selected) = 0 or 1; j-m (independently selected) = 0-100; Sia = mannose or mannose with mannose-6-phosphate.
```

1. mannosyltransferase, GDP-mannose-linker-ApoE

```
a-i = 0; q (independently selected) = 0 or 1; z = 1;
r-u (independently selected) = 0 or 1;
j-m (independently selected) = 0-100;
Sia = mannose or mannose with mannose-6-phosphate;
v-y (independently selected) = 0 or 1;
R = mannose-linker-ApoE.
```

FIG. 56F

```
CHO, BHK, 293 cells, Insect cells, Vero, yeast, fingi expressed alpha-galactosidase.

a-i, v-y = 0; q (independently selected) = 0 or 1; z = 1; r-u (independently selected) = 0 or 1; j-m (independently selected) = 0-100;

Sia = mannose or mannose with mannose-6-phosphate.
```

```
1. endo-H
2. galactosyltransferase,
UDP-Gal-linker-alpha2-macroglobulin
```

```
a-m, r-z=0; n, q (independently selected) = 0 or 1;
R' = galacotose-linker-alpha2-macroglobulin.
```

FIG 56G

```
Insect cell, yeast, fungi expressed alpha-galactosidase.
a-d, f, h, j-m, s, u, v-y = 0;
e, g, i, q, r, t (independently selected) = 0 or 1.

1. GNT-1,
UDP-GlcNAc-PEG-mannose-6-phosphate

e, i, q, r, v (independently selected) = 0 or 1;
a-d, f-h, j-n, s-u, w-y = 0; z = 1;
R = PEG-mannose-6-phosphate.
```

FIG. 56H

```
alpha-galactosidase.
a-d, f, h, j-m, s, u, v-y = 0;
e, g, i, q, r, t (independently selected) = 0 or 1.

1. GNT-1, UDP-GleNAc
2. galactosyltransferase,
UDP-Gal-PEG-transferrin

a, e, i, q, r, v (independently selected) = 0 or 1;
b-d, f-h, j-n, s-u, w-y = 0; z = 1;
R = PEG-transferrin
```

Insect cell, yeast, fungi expressed

FIG. 561

Insect cell, yeast, fungi expressed alpha-galactosidase.

a-d, f, h, j-m, s, u, v-y = 0;

e, g, i, q, r, t (independently selected) = 0 or 1.

1. GNT-1 and 2, UDP-GlcNAc

galactosyltransferase, UDP-Gal
 sialyltransferase,

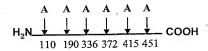
CMP-SA-PEG-melanotransferrin

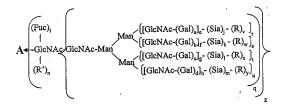
a, c, e, g, i, j, l, q, r, t, v, x (independently selected) = 0 or 1;

b, d, f, h, k, m, n, s, u, w, y = 0;

z = 1; R = PEG-melanotransferrin.

FIG. 56J





a-d, i, n, q-u, z (independently selected) = 0 or 1. e-h (independently selected) = 0 to 6. j-m (independently selected) = 0 to 100. v-y = 0 to 100; R = mannose, mannose-6-phosphate and mannose, polymer.

FIG. 57A

CHO, BHK, 293 cells, Insect cells, Vero expressed and secreted alpha-iduronidase
a-h, i-m, q-u (independently selected) = 0 or 1; z = 1;
n, v-y = 0; and when a-n = 0, then r-u (independently selected) = 0 or 1;
v-y (independently selected) = 0-100;
R = mannose or mannose with mannose-6-phosphate.

```
1. Endo-H
2. Galactosyltransferase, UDP-Gal-PEG-transferrin
```

a-h, i-m, q-u (independently selected) = 0 or 1; n, v-y = 0; z = 1; and when z = 0 and q = 1, then n (independently selected) = 0 or 1; R' = Gal-PEG-transferrin.

FIG. 57B

CHO, BHK, 293 cells, Insect cells, Vero expressed and secreted alpha-iduronidase a-h, i-m, q-u (independently selected) = 0 or 1; z = 1; n, v-y = 0; and when a-n = 0, then r-u (independently selected) = 0 or 1; v-y (independently selected) = 0-100; R = mannose or mannose with mannose-6-phosphate.

```
    Sialidase
    CMP-SA-linker-Mannose-6-phosphate ST3Gal3
```

FIG 57C

```
NSO expressed alpha-iduronidase. a-d, i-m, q-u (independently selected) = 0 or 1; e-h = 1; v-y=0; Sia (independently selected) = Sia or Gal.
```

- Sialidase and α-galactosidase
- 2. Galactosyltransferase, UDP-Gal
- ↓ 3. CMP-SA-linker-mannose-6-phosphate sialyltransferase

```
a-d, i-m, q-u (independently selected) = 0 or 1;
e-h = 1; v-y (independently selected) = 1,
when j-m (independently selected) is 1;
R = mannose-6 phosphate
```

FIG. 57D

```
CHO, BHK, 293 cells, Insect cells, Vero expressed and secreted alpha-iduronidase
a-h, i-m, q-u (independently selected) = 0 or 1; z = 1;
n, v-y = 0; and when a-n = 0, then r-u (independently selected) = 0 or 1;
v-y (independently selected) = 0-100;
R = mannose or mannose with mannose-6-phosphate.
```

- Sialidase
- CMP-SA-PEG, sialyltransferase

```
a-h, i-m, q-u, v-y (independently selected) = 0 or 1; n = 0; z = 1; R = PEG; and when a-n = 0, then r-u (independently selected) = 0 or 1; v-y = 0-100; R = mannose or mannose with mannose-6-phosphate.
```

FIG. 57E

```
CHO, BHK, 293 cells, Insect cells, Vero, yeast, fungi expressed alpha-iduronidase.

a-i, v-y = 0; q (independently selected) = 0 or 1; z = 1; r-u (independently selected) = 0 or 1; j-m (independently selected) = 0-100; Sia = mannose or mannose with mannose-6-phosphate.
```

```
1. mannosyltransferase,
GDP-mannose-linker-ApoE
```

```
a-i = 0; q (independently selected) = 0 or 1; z = 1;
r-u (independently selected) = 0 or 1; j-m (independently
selected) = 0-100;
Sia = mannose or mannose with mannose-6-phosphate;
v-y (independently selected) = 0 or 1;
R = mannose-linker-ApoE.
```

FIG. 57F

```
CHO, BHK, 293 cells, Insect cells, Vero, yeast, fungi expressed alpha-iduronidase.

a-i, v-y = 0; q (independently selected) = 0 or 1; z = 1; r-u (independently selected) = 0 or 1; j-m (independently selected) = 0-100; Sia = mannose or mannose with mannose-6-phosphate.
```

```
    1. endo-H
    2. galactosyltransferase,
    UDP-Gal-linker-alpha2-macroglobulin
```

```
a-m, r-z=0; n, q (independently selected) = 0 or 1; R' = galacotose-linker-alpha2-macroglobulin.
```

FIG. 57G

a-d, f-h, j-n, s-u, w-y = 0; z = R = PEG-mannose-6-phosphate.

Insect cell, yeast, fungi expressed

R = PEG-transferrin.

FIG. 57H

```
alpha-iduronidase.
a-d, f, h, j-m, s, u, v-y = 0;
e, g, i, q, r, t (independently selected) = 0 or 1.

| 1. GNT-1, UDP-GlcNAc
| 2. galactosyltransferase,
v UDP-Gal-PEG-transferrin
| a, e, i, q, r, v (independently selected) = 0 or 1;
b-d, f-h, j-n, s-u, w-y = 0; z = 1;
```

FIG. 571

Insect cell, yeast, fungi expressed alpha-iduronidase.
a-d, f, h, j-m, s, u, v-y = 0;
e, g, i, q, r, t (independently selected) = 0 or 1.

- 1. GNT-1 and 2, UDP-GlcNAc
 2. galactosyltransferase, UDP-Gal
 3. sialyltransferase,
 CMP-SA-PEG-melanotransferrin
- a, c, e, g, i, j, l, q, r, t, v, x (independently selected) = 0 or 1; b, d, f, h, k, m, n, s, u, w, y = 0; z = 1; R = PEG-melanotransferrin.

FIG. 57J

FIG. 58A

FIG. 58B

Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Cln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gln Leu Gln Pro Ala Phe Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Gln Pro

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GCGCCTCTTATGTACCCACAAAAATCTATTTTCAAAAAAGTTGCTCTA AGAATATAGTTATCAAGTTAAGTAAAATGTCAATAGCCTTTTAATTTA ATTTTTAATTGTTTTATCATTCTTTGCAATAATAAAACATTAACTTTAT ACTTTTTAATTTAATGTATAGAATAGAGATATACATAGGATATGTAAA TAGATACACAGTGTATATGTGATTAAAATATAATGGGAGATTCAATC AATAATGAAAAAAATGTGGTGAGAAAAACAGCTGAAAACCCATGTA AAGAGTGTATAAAGAAAGCAAAAAGAGAAGTAGAAAGTAACACAGG GGCATTTGGAAAATGTAAACGAGTATGTTCCCTATTTAAGGCTAGGC ACAAAGCAAGGTCTTCAGAGAACCTGGAGCCTAAGGTTTAGGCTCAC CCATTTCAACCAGTCTAGCAGCATCTGCAACATCTACAATGGCCTTGA CCTTTGCTTTACTGGTGCCCTCCTGGTGCTCAGCTGCAAGTCAAGCT GCTCTGTGGGCTGTGATCTGCCTCAAACCCACAGCCTGGGTAGCAGG AGGACCTTGATGCTCCTGGCACAGATGAGGAGAATCTCTCTTTTCTCC TGCTTGAAGGACAGACATGACTTTGGATTTCCCCAGGAGGAGTTTGG CAACCAGTTCCAAAAGGCTGAAACCATCCCTGTCCTCCATGAGATGA TCCAGCAGATCTTCAATCTCTTCAGCACAAAGGACTCATCTGCTGCTT GGGATGAGACCCTCCTAGACAAATTCTACACTGAACTCTACCAGCAG CTGAATGACCTGGAAGCCTGTGTGATACAGGGGGTGGGGGTGACAGA GACTCCCCTGATGAAGGAGGACTCCATTCTGGCTGTGAGGAAATACT TCCAAAGAATCACTCTCTATCTGAAAGAGAAGAAATACAGCCCTTGT GCCTGGGAGGTTGTCAGAGCAGAAATCATGAGATCTTTTTCTTTGTCA ACAAACTTGCAAGAAAGTTTAAGAAGTAAGGAATGAAAACTGGTTCA ACATGGAAATGATTTCATTGATTCGTATGCCAGCTCACCTTTTTATG ATCTGCCATTTCAAAGACTCATGTTTCTGCTATGACCATGACACGATT TAAATCTTTTCAAATGTTTTTAGGAGTATTAATCAACATTGTATTCAG ATCTATTTAAATATTTTTAAAATATTATTTATTTAACTATTTATAAAAAC AACTTATTTTTGTTCATATTATGTCATGTGCACCTTTGCACAGTGGTTA CATTGAACTTTTGCTATGGAACTTTTGTACTTGTTTATTCTTTAAAATG AAATTCCAAGCCTAATTGTGCAACCTGATTACAGAATAACTGGTACA TTTCTGTAAACCAAGTTGTATGTTGTACTCAAGATAACAGGGTGAACC TAACAAATACAATTCTGCTCTCTTGTGTATTTGATTTTTGTATGAAAA AAACTAAAAATGGTAATCATACTTAATTATCAGTTATGGTAAATGGT ATGA AGA GA AGA AGGA ACG

FIG. 59B

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Met Ala Leu Thr Phe Ala Leu Leu Val Ala Leu Leu Val Leu Ser Cys Lys Ser Ser Cys Ser Val Giy Cys Asp Leu Pro Gin Thr His Ser Leu Giy Ser Arg Arg Thr Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg His Asp Phe Giy Phe Pro Gin Glu Glu Phe Giy Asn Gln Phe Gin Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Gln Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Glu Thr Pro Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu Arg Ser Lys Glu

FIG. 59C

FIG. 59D

Met Ala Leu Leu Phe Pro Leu Leu Ala Ala Leu Val Met Thr Ser Tyr Ser Pro Val Gly Ser Leu Gly Cys Asp Leu Pro Gln Asn His Gly Leu Leu Ser Arg Asn Thr Leu Val Leu Leu His Gln Met Arg Arg He Ser Pro Phe Leu Cys Leu Lys Asp Arg Arg Asp Phe Arg Phe Pro Gln Glu Met Val Lys Gly Ser Gln Leu Gln Lys Ala His Val Met Ser Val Leu His Glu Met Leu Gln Gln Ile Phe Ser Leu Phe His Thr Glu Arg Ser Ser Ala Ala Trp Asn Met Thr Leu Leu Asp Gln Leu His Thr Gly Leu

FIG. 60A

ATGACCAACAAGTGTCTCCCCAAATTGCTCTCCTGTTGTGCTTCTCC ACTACAGCTCTTTCCATGAGCTACAACTTGCTTGGATTCCTACAAAGA AGCAGCAATTTTCAGTGTCAGAAGCTCCTGTGGCAATTGAATGGGAG GCTTGAATATTGCCTCAAGGACAGGATGAACTTTGACATCCCTGAGG AGATTAAGCAGCTGCAGCAGTTCCAGAAGGAGGACGCCGCATTGACC ATCTATGAGATGCTCCAGAACATCTTTGCTATTTTCAGACAAGATTCA TCTAGCACTGGCTGGAATGAGACTATTGTTGAGAACCTCCTGGCTAA TGTCTATCATCAGATAAACCATCTGAAGACAGTCCTGGAAGAAAAAC TGGAGAAAGAAGATTTTACCAGGGGAAAACTCATGAGCAGTCTGCAC CTGAAAAGATATTATGGGAGGATTCTGCATTACCTGAAGGCCAAGGA GTACAGTCACTGTGCCTGGACCATAGTCAGAGTGGAAATCCTAAGGA ACTTTTACTTCATTAACAGACTTACAGGTTACCTCCGAAACTGAAGAT CTCCTAGCCTGTCCCTCTGGGACTGGACAATTGCTTCAAGCATTCTTC AACCAGCAGATGCTGTTTAAGTGACTGATGGCTAATGTACTGCAAAT GAAAGGACACTAGAAGATTTTGAAATTTTTATTAAATTATGAGTTATT TTTATTTAT TTAAATTTTATTTTGGAAAATAAATTATTTTTGGTGC

FIG. 60B

Met Thr Asn Lys Cys Leu Leu Gin Ile Ala Leu Leu Leu Cys Phe Ser Thr Thr Ala Leu Ser Met Ser Tyr Asn Leu Leu Gly Phe Leu Gin Arg Ser Ser Asn Phe Gin Cys Gin Lys Leu Leu Trp Gin Leu Asn Gly ArgLeu Gin Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Giu Giu Ile Lys Gin Leu Gin Gin Phe Gin Lys Glu Asp Ala Leu Thr Ile Tyr Giu Met Leu Gin Asn Ile Phe Ala Ile Phe Arg Gin Asp Ser Ser Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gin Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn

FIG. 61A

ATGGTCTCCCAGGCCCTCAGGCTCCTCTGCCTTCTGCTTGGGCTTCAG GGCTGCCTGGCTGCAGTCTTCGTAACCCAGGAGGAAGCCCACGGCGT CCTGCACCGGCGCGCGCGCCAACGCGTTCCTGGAGGAGCTGCGGC CGGGCTCCCTGGAGAGGAGTGCAAGGAGGAGCAGTGCTCCTTCGA GGAGGCCCGGGAGATCTTCAAGGACGCGGAGAGGACGAAGCTGTTC TGGATTTCTTACAGTGATGGGGACCAGTGTGCCTCAAGTCCATGCCA GAATGGGGGCTCCTGCAAGGACCAGCTCCAGTCCTATATCTGCTTCT GCCTCCCTGCCTTCGAGGGCCGGAACTGTGAGACGCACAAGGATGAC CAGCTGATCTGTGAACGAGAACGGCGGCTGTGAGCAGTACTGCAG TGACCACACGGGCACCAAGCGCTCCTGTCGGTGCCACGAGGGGTACT CTCTGCTGGCAGACGGGGTGTCCTGCACACCCACAGTTGAATATCCA TGTGGAAAAATACCTATTCTAGAAAAAAGAAATGCCAGCAAACCCCA AGGCCGAATTGTGGGGGGCAAGGTGTCCCCAAAGGGGAGTGTCCA TGGCAGGTCCTGTTGTTGGTGAATGGAGCTCAGTTGTGTGGGGGGAC CCTGATCAACACCATCTGGGTGGTCTCCGCGGCCCACTGTTTCGACAA AATCAAGAACTGGAGGAACCTGATCGCGGTGCTGGGCGAGCACGAC CTCAGCGAGCACGACGGGGATGAGCAGAGCCGGCGGGTGGCGCAGG GCGCTGCTCCGCCTGCACCAGCCCGTGGTCCTCACTGACCATGTGGTG CCCCTCTGCCTGCCCGAACGGACGTTCTCTGAGAGGACGCTGGCCTTC GTGCGCTTCTCATTGGTCAGCGGCTGGGGCCAGCTGCTGGACCGTGG CGCCACGGCCTGGAGCTCATGGTGCTCAACGTGCCCCGGCTGATGA CCCAGGACTGCCTGCAGCAGTCACGGAAGGTGGGAGACTCCCCAAAT ATCACGGAGTACATGTTCTGTGCCGGCTACTCGGATGGCAGCAAGGA CTCCTGCAAGGGGACAGTGGAGGCCCACATGCCACCCACTACCGGG GCACGTGGTACCTGACGGGCATCGTCAGCTGGGGCCAGGGCTGCGCA ACCGTGGGCCACTTTGGGGTGTACACCAGGGTCTCCCAGTACATCGA GTGGCTGCAAAAGCTCATGCGCTCAGAGCCACGCCCAGGAGTCCTCC TGCGAGCCCCATTTCCC

FIG. 61B

Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln Gly Cys Leu Ala Ala Val Phe Val Thr Gln Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp lle Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro Phe Pro

FIG. 62A

ATGCAGCGCGTGAACATGATCATGGCAGAATCACCAAGCCTCATCAC CATCTGCCTTTTAGGATATCTACTCAGTGCTGAATGTACAGTTTTTCTT GATCATGAAAACGCCAACAAAATTCTGAATCGGCCAAAGAGGTATAA GTATGGAAGAAAGTGTAGTTTTGAAGAACCACGAGAAGTTTTTGAA AACACTGAAAAGACAACTGAATTTTGGAAGCAGTATGTTGATGGAGA TCAGTGTGAGTCCAATCCATGTTTAAATGGCGGCAGTTGCAAGGATG ACATTAATTCCTATGAATGTTGGTGTCCCTTTGGATTTGAAGGAAAGA ACTGTGAATTAGATGTAACATGTAACATTAAGAATGGCAGATGCGAG CAGTTTTGTAAAAATAGTGCTGATAACAAGGTGGTTTGCTCCTGTACT GAGGGATATCGACTTGCAGAAAACCAGAAGTCCTGTGAACCAGCAGT GCCATTTCCATGTGGAAGAGTTTCTGTTTCACAAACTTCTAAGCTCAC CCGTGCTGAGGCTGTTTTTCCTGATGTGGACTATGTAAATCCTACTGA AGCTGAAACCATTTTGGATAACATCACTCAAGGCACCCAATCATTTA ATGACTTCACTCGGGTTGTTGGTGGAGAAGATGCCAAACCAGGTCAA TTCCCTTGGCAGGTTGTTTTGAATGGTAAAGTTGATGCATTCTGTGGA GGCTCTATCGTTAATGAAAAATGGATTGTAACTGCTGCCCACTGTGTT GAAACTGGTGTTAAAATTACAGTTGTCGCAGGTGAACATAATATTGA GGAGACAGAACATACAGAGCAAAAGCGAAATGTGATTCGAGCAATT ATTCCTCACCACAACTACAATGCAGCTATTAATAAGTACAACCATGA CATTGCCCTTCTGGAACTGGACGAACCCTTAGTGCTAAACAGCTACG TTACACCTATTTGCATTGCTGACAAGGAATACACGAACATCTTCCTCA AATTTGGATCTGGCTATGTAAGTGGCTGGGCAAGAGTCTTCCACAAA GGGAGATCAGCTTTAGTTCTTCAGTACCTTAGAGTTCCACTTGTTGAC CGAGCCACATGTCTTCGATCTACAAAGTTCACCATCTATAACAACAT GTTCTGTGCTGGCTTCCATGAAGGAGGTAGAGATTCATGTCAAGGAG ATAGTGGGGGACCCCATGTTACTGAAGTGGAAGGGACCAGTTTCTTA ACTGGAATTATTAGCTGGGGTGAAGAGTGTGCAATGAAAGGCAAATA TGGAATATATACCAAGGTATCCCGGTATGTCAACTGGATTAAGGAAA AAACAAAGCTCACTTAATGAAAGATGGATTTCCAAGGTTAATTCATT GGAATTGAAAATTAACAG

FIG. 62B

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Ser Leu Ile Thr Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe LeuAsp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys Met Glu Glu Lys Cys Ser Phe Glu Glu Pro Arg Glu Val Phe Glu Asn Thr Glu Lys Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe Pro Cys Gly Arg Val Ser Val Ser Gln Thr Ser Lys Leu Thr Arg Ala Glu Ala Val Phe Pro Asp Val Asp Tyr Val Asn Pro Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile Thr Gln Gly Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg Ala Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asp Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Ala Arg Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Arg Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cvs Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr

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FIG. 63A

FIG. 63B

Met Asp Tyr Tyr Arg Lys Tyr Ala Ala Ile Phe Leu Val Thr Leu Ser Val Phe Leu His Val Leu His Ser Ala Pro Asp Val Gln Asp Cys Pro Glu Cys Thr Leu Gln Glu Asn Pro Phe Phe Ser Gln Pro Gly Ala Pro Ile Leu Gln Cys Met Gly Cys Cys Phe Ser Arg Ala Tyr Pro Thr Pro Leu Arg Ser Lys Lys Thr Met Leu Val Gln Lys Asn Val Thr Ser Glu Ser Thr Cys Cys Val Ala Lys Ser Tyr Asn Arg Val Thr Val Met Gly Gly Phe Lys Val Glu Asn His Thr Ala Cys His Cys Ser Thr Cys Tyr Tyr His Lys Ser

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FIG. 63C

FIG. 63D

Met Lys Thr Leu Gln Phe Phe Phe Leu Phe Cys Cys Trp Lys Ala Ile Cys Cys Asn Ser Cys Glu Leu Thr Asn Ile Thr Ile Ala Ile Glu Lys Glu Glu Cys Arg Phe Cys Ile Ser Ile Asn Thr Thr Trp Cys Ala Gly Tyr Cys Tyr Thr Arg Asp Leu Val Tyr Lys Asp Pro Ala Arg Pro Lys Ile Gln Lys Thr Cys Thr Phe Lys Glu Leu Val Tyr Glu Thr Val Arg Val Pro Gly Cys Ala His His Ala Asp Ser Leu Tyr Thr Tyr Pro Val Ala Thr Gln Cys His Cys Gly Lys Cys Asp Ser Asp Ser Thr Asp Cys Thr Val Arg Gly Leu Gly Pro Ser Tyr Cys Ser Phe Gly Glu Met Lys Glu

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FIG. 64A

CCCGGAGCCGGGCCACCGCGCCCGCTCTGCTCCGACACCGC GCCCCTGGACAGCCGCCCTCTCCTCCAGGCCCGTGGGGCTGGCCCT GCACCGCGAGCTTCCCGGGATGAGGGCCCCCGGTGTGGTCACCCGG CGCGCCCAGGTCGCTGAGGGACCCCGGCCAGGCGCGAGATGGGG GTGCACGAATGTCCTGCCTGGCTGTGGCTTCTCCTGTCCCTGCTGTCG CTCCCTCTGGGCCTCCCAGTCCTGGGCGCCCCACCACGCCTCATCTGT GACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGGCCG AGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAAT ATCACTGTCCCAGACACCAAAGTTAATTTCTATGCCTGGAAGAGGAT GGAGGTCGGGCAGCAGGCCGTAGAAGTCTGGCAGGGCCTGGCCCTG CTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCC CAGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGG CCTTCGCAGCCTCACCACTCTGCTTCGGGCTCTGCGAGCCCAGAAGG AAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCTCCACTCCGAACA ATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTC CTCCGGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAG GGGACAGATGACCAGGTGTGTCCACCTGGGCATATCCACCACCTCCC TCACCAACATTGCTTGTGCCACACCCTCCCCGCCACTCCTGAACCCC GTCGAGGGGCTCTCAGCTCAGCGCCAGCCTGTCCCATGGACACTCCA GTGCCAGCAATGACATCTCAGGGGCCAGAGGAACTGTCCAGAGAGC AACTCTGAGATCTAAGGATGTCACAGGGCCAACTTGAGGGCCCAGAG CAGGAAGCATTCAGAGAGCAGCTTTAAACTCAGGGACAGAGCCATG CTGGGAAGACGCCTGAGCTCACTCGGCACCCTGCAAAATTTGATGCC AGGACACGCTTTGGAGGCGATTTACCTGTTTTCGCACCTACCATCAGG GACAGGATGACCTGGAGAACTTAGGTGGCAAGCTGTGACTTCTCCAG GTCTCACGGGCATGGGCACTCCCTTGGTGGCAAGAGCCCCCTTGACA CCGGGGTGGTGGGAACCATGAAGACAGGATGGGGGCTGGCCTCTGG CTCTCATGGGGTCCAAGTTTTGTGTATTCTTCAACCTCATTGACAAGA ACTGAAACCACCAAAAAAAAAAAAAA

FIG. 64B

Met Gly Val His Glu Cys Pro Ala Trp Leu Trp Leu Leu Leu Ser Leu Leu Ser Leu Pro Leu Gly Leu Pro Val Leu Gly Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Gly Ala Pro Pro Arg Leu Ile Cys Asp Ser Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Arg Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg

FIG. 65

Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp

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FIG. 66A

ATGTGGCTGCAGAGCCTGCTGCTCTTGGGCACTGTGGCCTGCAGCAT
CTCTGCACCCGCCGCTCGCCCAGCCCCAGCACCACCAGCACCTTGCAGCAG
ATGTGAATGCCATCCAGGAGGCCCGCGCTTCCCTGAACCTGAGTAGA
GACACTGCTGCTGAGATGAATGAAACAGTAGAAGTCATCTCAGAAAT
GTTTGACCTCCAGGAGCCGACCTGCCTACAGAACCCGCCTGGAGCTGT
ACAAGCAGGGCCTGCGGGGCAGCCTCACCAAGCTCAAGGGCCCTTG
ACATTGATGGCCAGCCACTACAAGCAGCACTGCCCTCCAACCCGGA
AACTTCCTGTGCAACCCAGATTATCACCTTTGAAAGTTTCAAAGAGA
ACCTGAAGGACTTTCTGCTTGTTCATCCCTTTGACTGCTGGGAGCCAG
TCCAGGAGTGA

FIG. 66B

Met Trp Leu Gin Ser Leu Leu Leu Leu Gly Thr Val Ala Cys Ser Ile Ser Ala Pro Ala Arg Ser Pro Ser Pro Ser Thr Gin Pro Trp Glu His Val Asn Ala Ile Gin Glu Ala Arg Arg Leu Leu Asn Leu Ser Arg Asp Thr Ala Ala Glu Met Asn Glu Thr Val Glu Val Ile Ser Glu Met Phe Asp Leu Gln Glu Pro Thr Cys Leu Gln Thr Arg Leu Glu Leu Tyr Lys Gln Gly Leu Arg Gly Ser Leu Thr Lys Leu Lys Gly Pro Leu Thr Met Met Ala Ser His Tyr Lys Gln His Cys Pro Pro Thr Pro Glu Thr Ser Cys Ala Thr Gln Ile Ile Thr Phe Glu Ser Phe Lys Glu Asn Leu Lys Asp Phe Leu Val Ile Pro Phe Asp Cys Trp Glu Pro Val Gln Glu

FIG. 67A

ATGAAATATACAAGTTATATCTTGGCTTTTCAGCTCTGCATCGTTTTG
GGTTCTCTTGGCTGTTACTGCCAGGACCCATATGTAAAAGAAGCAGA
AAACCTTAAGAAATAATTTAATGCAGGTCATTCAGATGTAAGAGGGATA
ATGGAACTCTTTTCTTAGGCATTTTGAAGAATTGGAAAGAGGAGG
GACAGAAAAATAATGCAGAGCCCAAATTGTCTCCTTTTACTTCAAACT
TTTTAAAAACTTTAAAGATGACCAGAGCATCCAAAAGAGTGTGGAGA
CCATCAAGGAAGACATGAATGTCAAGTTTTTCAATAGCAACAAAAAA
AAACGAGATGACTTCGAAAAGCTGACTAATTATTCGGTAACTGACTT
GAATGTCCAACGCAAAGCAATACATGAACTCATCCAAGTGATGGCTG
AACTGTCGCCAGCAGCTAAAAACAGGGAACCGAAAAAAGGAGTCAGAT
GCTGTTTCGAGGTCGAAGAGCATCCCAGTAA

FIG. 67B

Met Lys Tyr Thr Ser Tyr Ile Leu Ala Phe Gin Leu Cys Ile Val Leu Gly Ser Leu Gly Cys Tyr Cys Gin Asp Pro Tyr Val Lys Gin Ala Giu Asn Leu Lys Lys Tyr Phe Asn Ala Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe Leu Gly Ile Leu Lys Asn Trp Lys Glu Glu Ser Asp Arg Lys Ile Met Gin Ser Gin Ile Val Ser Phe Tyr Phe Lys Leu Phe Lys Asn Phe Lys Asp Asp Gin Ser Ile Gin Lys Ser Val Glu Thr Ile Lys Glu Asp Met Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala Ile His Giu Leu Ile Gin Val Met Ala Glu Leu Ser Pro Ala Ala Lys Thr Gly Lys Arg Lys Arg Ser Gin Met Leu Phe Arg Gly Arg Arg Ala Ser Gin

FIG. 68A

CTGGGACAGTGAATCGACAATGCCGTCTTCTGTCTCGTGGGGCATCCT CCTGCTGGCAGGCCTGTGCTGCCTGGTCCCTGTCTCCCTGGCTGAGGA TCCCCAGGGAGATGCTGCCCAGAAGACAGATACATCCCACCATGATC AGGATCACCCAACCTTCAACAAGATCACCCCCAACCTGGCTGAGTTC GCCTTCAGCCTATACCGCCAGCTGGCACACCAGTCCAACAGCACCAA TATCTTCTCCCCCAGTGAGCATCGCTACAGCCTTTGCAATGCTCTC CCTGGGGACCAAGGCTGACACTCACGATGAAATCCTGGAGGGCCTGA ATTTCAACCTCACGGAGATTCCGGAGGCTCAGATCCATGAAGGCTTC GACCACCGGCAATGGCCTGTTCCTCAGCGAGGGCCTGAAGCTAGTGG ATAAGTTTTTGGAGGATGTTAAAAAGTTGTACCACTCAGAAGCCTTC ACTGTCAACTTCGGGGACACCGAAGAGGGCCAAGAAACAGATCAACG ATTACGTGGAGAAGGGTACTCAAGGGAAAATTGTGGATTTGGTCAAG GAGCTTGACAGAGACACAGTTTTTGCTCTGGTGAATTACATCTTCTTT AAAGGCAAATGGGAGAGACCCTTTGAAGTCAAGGACACCGAGGAAG AGGACTTCCACGTGGACCAGGTGACCACCGTGAAGGTGCCTATGATG AAGCGTTTAGGCATGTTTAACATCCAGCACTGTAAGAAGCTGTCCAG CTGGGTGCTGATGAAATACCTGGGCAATGCCACCGCCATCTTCT TCCTGCCTGATGAGGGGAAACTACAGCACCTGGAAAATGAACTCACC CACGATATCATCACCAAGTTCCTGGAAAATGAAGACAGAAGGTCTGC CAGCTTACATTTACCCAAACTGTCCATTACTGGAACCTATGATCTGAA GAGCGTCCTGGGTCAACTGGGCATCACTAAGGTCTTCAGCAATGGGG CTGACCTCTCCGGGGTCACAGAGGAGGCACCCCTGAAGCTCTCCAAG GCCGTGCATAAGGCTGTGCTGACCATCGACGAGAAAGGGACTGAAGC TGCTGGGGCCATGTTTTTAGAGGCCATACCCATGTCTATCCCCCCGA GGTCAAGTTCAACAAACCCTTTGTCTTCTTAATGATTGAACAAAATAC AACTGCCTCTCGCTCCTCAACCCCTCCCTCCATCCCTGGCCCCCTCC CTGGATGACATTAAAGAAGGGTTGAGCTGG

FIG. 68B

Met Pro Ser Ser Val Ser Trp Gly Ile Leu Leu Leu Ala Gly Leu Cys Cys Leu Val Pro Val Ser Leu Ala Glu Asp Pro Gln Gly Asp Ala Ala Gln Lys Thr Asp Thr Ser His His Asp Gln Asp His Pro Thr Phe Asn Lys Ile Thr Pro Asn Leu Ala Glu Phe Ala Phe Ser Leu Tyr Arg Gln Leu Ala His Gln Ser Asn Ser Thr Asn Ile Phe Phe Ser Pro Vai Ser Ile Ala Thr Ala Phe Ala Met Leu Ser Leu Gly Thr Lys Ala Asp Thr His Asp Glu Ile Leu Glu Gly Leu Asn Phe Asn Leu Thr Glu Ile Pro Glu Ala Gin Ile His Glu Gly Phe Gin Glu Leu Leu Arg Thr Leu Asn Gin Pro Asp Ser Gin Leu Gin Leu Thr Thr Gly Asn Gly Leu Phe Leu Ser Glu Gly Leu Lys Leu Val Asp Lys Phe Leu Glu Asp Val Lys Lys Leu Tyr His Ser Glu Ala Phe Thr Val Asn Phe Gly Asp Thr Glu Glu Ala Lys Lys Gln Ile Asn Asp Tyr Val Glu Lys Gly Thr Gln Gly Lys Ile Val Asp Leu Val Lys Glu Leu Asp Arg Asp Thr Val Phe Ala LeuVal Asn Tyr Ile Phe Phe Lys Gly Lys Trp Glu Arg Pro Phe Glu Val Lys Asp Thr Glu Glu Glu Asp Phe His Val Asp Gln Val Thr Thr Val Lys Val Pro Met Met Lys Arg Leu Gly Met Phe Asn Ile Gln His Cys Lys Lys Leu Ser Ser Trp Val Leu Leu Met Lys Tyr Leu Gly Asn Ala Thr Ala Ile Phe Phe Leu Pro Asp Glu Gly Lys Leu Gln His Leu Glu Asn Glu Leu Thr His Asp Ile Ile Thr Lys Phe Leu Glu Asn Glu AspArg Arg Ser Ala Ser Leu His Leu Pro Lvs Leu Ser Ile Thr Gly Thr Tyr Asp Leu Lys Ser Val Leu Gly Gln Leu Gly Ile Thr Lys Val Phe Ser Asn Gly Ala Asp Leu Ser Gly Val Thr Glu Glu Ala Pro Leu Lys Leu Ser Lys Ala Val His Lys Ala Val Leu Thr Ile Asp Glu Lys Gly Thr Glu Ala Ala Gly Ala Met Phe Leu Glu Ala Ile Pro Met Ser Ile Pro Pro Glu Val Lys Phe Asn Lys Pro Phe Val Phe Leu Met Ile Glu Gln Asn Thr Lys Ser Pro Leu Phe Met Gly Lys Val Val Asn Pro Thr Gln Lys

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GCTAACCTAGTGCCTATAGCTAAGGCAGGTACCTGCATCCTTGTTTTT GTTTAGTGGATCCTCTATCCTTCAGAGACTCTGGAACCCCTGTGGTCT TCTCTTCATCTAATGACCCTGAGGGGATGGAGTTTTCAAGTCCTTCCA AGCCTCACAGGTTTGCTTCTACTTCAGGCAGTGTCGTGGGCATCAGGT GCCCGCCCTGCATCCCTAAAAGCTTCGGCTACAGCTCGGTGGTGTGT GTCTGCAATGCCACATACTGTGACTCCTTTGACCCCCCGACCTTTCCT GCCCTTGGTACCTTCAGCCGCTATGAGAGTACACGCAGTGGGCGACG GATGGAGCTGAGTATGGGGCCCATCCAGGCTAATCACACGGGCACAG GCCTGCTACTGACCCTGCAGCCAGAACAGAAGTTCCAGAAAGTGAAG GGATTTGGAGGGGCCATGACAGATGCTGCTGCTCTCAACATCCTTGCC CTGTCACCCCTGCCCAAAATTTGCTACTTAAATCGTACTTCTCTGAA GAAGGAATCGGATATAACATCATCCGGGTACCCATGGCCAGCTGTGA CTTCTCCATCCGCACCTACACCTATGCAGACACCCCTGATGATTTCCA GTTGCACAACTTCAGCCTCCCAGAGGAAGATACCAAGCTCAAGATAC CCCTGATTCACCGAGCCCTGCAGTTGGCCCAGCGTCCCGTTTCACTCC TTGCCAGCCCTGGACATCACCCACTTGGCTCAAGACCAATGGAGCG GTGAATGGGAAGGGGTCACTCAAGGGACAGCCCGGAGACATCTACC ACCAGACCTGGGCCAGATACTTTGTGAAGTTCCTGGATGCCTATGCTG AGCACAAGTTACAGTTCTGGGCAGTGACAGCTGAAAATGAGCCTTCT GCTGGGCTGTTGAGTGGATACCCCTTCCAGTGCCTGGGCTTCACCCCT GAACATCAGCGAGACTTCATTGCCCGTGACCTAGGTCCTACCCTCGCC AACAGTACTCACCACAATGTCCGCCTACTCATGCTGGATGACCAACGC TTGCTGCTGCCCCACTGGGCAAAGGTGGTACTGACAGACCCAGAAGC AGCTAAATATGTTCATGGCATTGCTGTACATTGGTACCTGGACTTTCT GGCTCCAGCCAAAGCCACCCTAGGGGAGACACACCGCCTGTTCCCCA ACACCATGCTCTTTGCCTCAGAGGCCTGTGTGGGCTCCAAGTTCTGGG AGCAGAGTGTGCGGCTAGGCTCCTGGGATCGAGGGATGCAGTACAGC CACAGCATCATCACGAACCTCCTGTACCATGTGGTCGGCTGGACCGAC TGGAACCTTGCCCTGAACCCCGAAGGAGGACCCAATTGGGTGCGTAA CTTTGTCGACAGTCCCATCATTGTAGACATCACCAAGGACACGTTTTA CAAACAGCCCATGTTCTACCACCTTGGCCACTTCAGCAAGTTCATTCC TGAGGGCTCCCAGAGAGTGGGGCTGGTTGCCAGTCAGAAGAACGACC TGGACGCAGTGGCACTGATGCATCCCGATGGCTCTGCTGTTGTGGTCG TGCTAAACCGCTCCTCTAAGGATGTGCCTCTTACCATCAAGGATCCTG CTGTGGGCTTCCTGGAGACAATCTCACCTGGCTACTCCATTCACACCT ACCTGTGGCATCGCCAGTGATGGAGCAGATACTCAAGGAGGCACTGG GCTCAGCCTGGGCATTAAAGGGACAGAGTCAGCTCACACGCTGTCTG TGACTAAAGAGGGCACAGCAGGGCCAGTGTGAGCTTACAGCGACGT

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FIG. 69A-2

FIG. 69B

Met Glu Phe Ser Ser Pro Ser Arg Glu Glu Cys Pro Lys Pro Leu Ser Arg Val Ser Ile Met Ala Gly Ser Leu Thr Gly Leu Leu Leu Leu Gln Ala Val Ser Trp Ala Ser Gly Ala Arg Pro Cys Ile Pro Lys Ser Phe Gly Tyr Ser Ser Val Val Cys Val Cys Asn Ala Thr Tyr Cys Asp Ser Phe Asp Pro Pro Thr Phe Pro Ala Leu Gly Thr Phe Ser Arg Tvr Glu Ser Thr Arg Ser Gly Arg Arg Met Glu Leu Ser Met Gly Pro Ile Gln Ala Asn His Thr Gly Thr Gly Leu Leu Leu Thr Leu Gln Pro Glu Gln Lys Phe Gln Lys Val Lys Gly Phe Gly Gly Ala Met Thr Asp Ala Ala Ala Leu Asn Ile Leu Ala Leu Ser Pro Pro Ala Gln Asn Leu Leu Leu Lys Ser Tyr Phe Ser Glu Glu Gly Ile Gly Tyr Asn Ile Ile Arg Val Pro Met Ala Ser Cys Asp Phe Ser Ile Arg Thr Tyr Thr Tyr Ala Asp Thr Pro Asp Asp Phe Gln Leu His Asn Phe Ser Leu Pro Glu Glu Asp Thr Lys Leu Lys Ile Pro Leu Ile His Arg Ala Leu Gln Leu Ala Gln Arg Pro Val Ser Leu Leu Ala Ser Pro Trp Thr Ser Pro Thr Trp Leu Lys Thr Asn Gly Ala Val Asn Gly Lys Gly Ser Leu Lys Gly Gln Pro Gly Asp Ile Tyr His Gln Thr Trp Ala Arg Tyr Phe Val Lys Phe Leu Asp Ala Tyr Ala Glu His Lys Leu Gln Phe Trp Ala Val Thr Ala Glu Asn Glu Pro Ser Ala Gly Leu Leu Ser Gly Tyr Pro Phe Gln Cys Leu Gly Phe Thr Pro Glu His Gln Arg Asp Phe Ile Ala Arg Asp Leu Gly Pro Thr Leu Ala Asn Ser Thr His His Asn Val Arg Leu Leu Met Leu Asp Asp Gln Arg Leu Leu Leu Pro His Trp Ala Lys Val Val Leu Thr Asp Pro Glu Ala Ala Lys Tyr Val His Gly Ile Ala Val His Trp Tyr Leu Asp Phe Leu Ala Pro Ala Lys Ala Thr Leu Gly Glu Thr His Arg Leu Phe Pro Asn Thr Met Leu Phe Ala Ser Glu Ala Cys Val Gly Ser Lys Phe Trp Glu Gln Ser Val Arg Leu Gly Ser Trp Asp Arg Gly Met Gln Tyr Ser His Ser Ile Ile Thr Asn Leu Leu Tyr His Val Val Gly Trp Thr Asp Trp Asn Leu Ala Leu Asn Pro Glu Gly Gly Pro Asn Trp Val Arg Asn Phe Val Asp Ser Pro Ile Ile Val Asp Ile Thr Lys Asp Thr Phe Tyr Lys Gln Pro Met Phe Tyr His Leu Gly His Phe Ser Lys Phe Ile Pro Glu Gly Ser Gln Arg Val Gly Leu Val Ala Ser Gln Lys Asn Asp Leu Asp Ala Val Ala Leu Met His Pro Asp Gly Ser Ala Val Val Val Val Leu Asn Arg Ser Ser Lys Asp Val Pro Leu Thr Ile Lys Asp Pro Ala Val Gly Phe Leu Glu Thr Ile Ser Pro Gly Tvr Ser Ile His Thr Tyr Leu Trp His Arg Gln

FIG. 70A

ATGGATGCAATGAAGAGAGGGCTCTGCTGTGTGCTGCTGTGTGG AGCAGTCTTCGTTTCGCCCAGCCAGGAAATCCATGCCCGATTCAGAA GAGGAGCCAGATCTTACCAAGTGATCTGCAGAGATGAAAAAACGCA GATGATATACCAGCAACATCAGTCATGGCTGCGCCCTGTGCTCAGAA GCAACCGGGTGGAATATTGCTGGTGCAACAGTGGCAGGGCACAGTGC CACTCAGTGCCTGTCAAAAGTTGCAGCGAGCCAAGGTGTTTCAACGG GGGCACCTGCCAGCAGGCCCTGTACTTCTCAGATTTCGTGTGCCAGTG CCCGAAGGATTTGCTGGGAAGTGCTGTGAAATAGATACCAGGGCCA CGTGCTACGAGGACCAGGGCATCAGCTACAGGGGCACGTGGAGCAC AGCGGAGAGTGGCGCCGAGTGCACCAACTGGAACAGCAGCGCGTTG GCCCAGAAGCCCTACAGCGGGCGGAGGCCAGACGCCATCAGGCTGG GCCTGGGGAACCACAACTACTGCAGAAACCCAGATCGAGACTCAAA GCCCTGGTGCTACGTCTTTAAGGCGGGGAAGTACAGCTCAGAGTTCT GCAGCACCCCTGCCTGCTCTGAGGGAAACAGTGACTGCTACTTTGGG AATGGGTCAGCCTACCGTGGCACGCACAGCCTCACCGAGTCGGGTGC CTCCTGCCTCCCGTGGAATTCCATGATCCTGATAGGCAAGGTTTACAC AGCACAGAACCCCAGTGCCCAGGCACTGGGCCTGGGCAAACATAATT ACTGCCGGAATCCTGATGGGGATGCCAAGCCCTGGTGCCACGTGCTG AAGAACCGCAGGCTGACGTGGGAGTACTGTGATGTGCCCTCCTGCTC CACCTGCGGCCTGAGACAGTACAGCCAGCCTCAGTTTCGCATCAAAG GAGGGCTCTTCGCCGACATCGCCTCCCACCCCTGGCAGGCTGCCATCT TTGCCAAGCACAGGAGGTCGCCGGGAGAGCGGTTCCTGTGCGGGGGC ATACTCATCAGCTCCTGCTGGATTCTCTCTGCCGCCCACTGCTTCCAG GAGAGGTTTCCGCCCCACCACCTGACGGTGATCTTGGGCAGAACATA CCGGGTGGTCCCTGGCGAGGAGGAGCAGAAATTTGAAGTCGAAAAA TACATTGTCCATAAGGAATTCGATGATGACACTTACGACAATGACAT TGCGCTGCTGCAGCTGAAATCGGATTCGTCCCGCTGTGCCCAGGAGA GCAGCGTGGTCCGCACTGTGTGCCTTCCCCCGGCGGACCTGCAGCTG CCGGACTGGACGGAGTGTGAGCTCTCCGGCTACGGCAAGCATGAGGC CTTGTCTCCTTTCTATTCGGAGCGGCTGAAGGAGGCTCATGTCAGACT GTACCCATCCAGCCGCTGCACATCACAACATTTACTTAACAGAACAG TCACCGACAACATGCTGTGTGCTGGAGACACTCGGAGCGGCGGGCCC CAGGCAAACTTGCACGACGCCTGCCAGGGCGATTCGGGAGGCCCCCT GGTGTGTCTGAACGATGGCCGCATGACTTTGGTGGGCATCATCAGCT GGGGCCTGGGCTGTGGACAGAAGGATGTCCCGGGTGTGTACACCAAG GTTACCAACTACCTAGACTGGATTCGTGACAACATGCGACCGTGACC AGGAACACCCGACTCCTCAAAAGCAAATGAGATCC

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FIG. 70B

Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly Ala Val Phe Val Ser Pro Ser Gln Glu Ile His Ala Arg Phe Arg Arg Gly Ala Arg Ser Tyr Gln Val Ile Cys Arg Asp Glu Lys Thr Gln Met Ile Tyr Gln Gln His Gin Ser Trp Leu Arg Pro Val Leu Arg Ser Asn Arg Val Glu Tyr Cys Trp Cys Asn Ser Gly Arg Ala Gln Cys His Ser Val Pro Val Lys Ser Cys Ser Glu Pro Arg Cys Phe Asn Gly Gly Thr Cys Gin Gin Ala Leu Tyr Phe Ser Asp Phe Vai Cys Gin Cys Pro Glu Gly Phe Ala Gly Lys Cys Cys Glu Ile Asp Thr Arg Ala Thr Cys Tyr Glu Asp Gln Gly Ile Ser Tyr Arg Gly Thr Trp Ser Thr Ala Glu Ser Gly Ala Glu Cys Thr Asn Trp Asn Ser Ser Ala Leu Ala Gln Lys Pro Tyr Ser Gly Arg Arg Pro Asp Ala Ile Arg Leu Gly Leu Gly Asn His Asn Tyr Cys Arg Asn Pro Asp Arg Asp Ser Lys Pro Trp Cys Tyr Val Phe Lys Ala Gly Lys Tyr Ser Ser Glu Phe Cys Ser Thr Pro Ala Cys Ser Glu Gly Asn Ser Asp Cys Tyr Phe Gly Asn Gly Ser Ala Tyr Arg Gly Thr His Ser Leu Thr Glu Ser Gly Ala Ser Cys Leu Pro Trp Asn Ser Met Ile Leu Ile Gly Lys Val Tyr Thr Ala Gln Asn Pro Ser Ala Gln Ala Leu Gly Leu Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Gly Asp Ala Lys Pro Trp Cys His Val Leu Lys Asn Arg Arg Leu Thr Trp Glu Tyr Cys Asp Val Pro Ser Cys Ser Thr Cys Gly Leu Arg Gln Tyr Ser Gln Pro Gln Phe Arg Ile Lys Gly Gly Leu Phe Ala Asp Ile Ala Ser His Pro Trp Gln Ala Ala Ile Phe Ala Lys His Arg Arg Ser Pro Gly Glu Arg Phe Leu Cys Gly Gly Ile Leu Ile Ser Ser Cys Trp Ile Leu Ser Ala Ala His Cys Phe Gin Glu Arg Phe Pro Pro His His Leu Thr Val Ile Leu Gly Arg Thr Tyr Arg Val Val Pro Gly Glu Glu Glu Gln Lys Phe Glu Val Glu Lys Tyr Ile Val His Lys Glu Phe Asp Asp Asp Thr Tyr Asp Asn Asp Ile Ala Leu Leu Gln Leu Lys Ser Asp Ser Ser Arg Cys Ala Gln Glu Ser Ser Val Val Arg Thr Val Cys Leu Pro Pro Ala Asp Leu Gln Leu Pro Asp Trp Thr Glu Cys Glu Leu Ser Gly Tyr Gly Lys His Glu Ala Leu Ser Pro Phe Tyr Ser Glu Arg Leu Lys Glu Ala His Val Arg Leu Tyr Pro Ser Ser Arg Cys Thr Ser Gln His Leu Leu Asn Arg Thr Val Thr Asp Asn Met Leu Cys Ala Gly Asp Thr Arg Ser Gly Gly Pro Gln Ala Asn Leu His Asp Ala Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Leu Asn Asp Gly Arg Met Thr Leu Val Gly Ile Ile Ser Trp Gly Leu Gly Cys Gly Gln Lys Asp Val Pro Gly Val Tyr Thr Lys Val Thr Asn Tyr Leu Asp Trp Ile Arg Asp Asn Met Arg Pro

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FIG. 71A

ATCACTCTCTTTAATCACTACTCACATTAACCTCAACTCCTGCCACAA TGTACAGGATGCAACTCCTGTCTTGCATTGCACTAATTCTTGCACTTG ACACAGCTACAACTGGAGCATTTACTGCTGGATTTACAGATGATTTTG AATGGAATTAATAATTACAAGAATCCCAAACTCACCAGGATGCTCAC ATTTAAGTTTTACATGCCCAAGAAGGCCACAGAACTGAAACAGCTTC AGTGTCTAGAAGAAGAACTCAAACCTCTGGAGGAAGTGCTGAATTTA GCTCAAAGCAAAAACTTTCACTTAAGACCCAGGGACTTAATCAGCAA TATCAACGTAATAGTTCTGGAACTAAAGGGATCTGAAACAACATTCA TGTGTGAATATGCAGATGAGACAGCAACCATTGTAGAATTTCTGAAC AGATGGATTACCTTTTGTCAAAGCATCATCTCAACACTAACTTGATAA AATATTTAAATTTTATTTTATTGTTGAATGTATGGTTGCTACCTATTG TAACTATTATTCTTAATCTTAAAACTATAAATATGGATCTTTTATGAT CAAAAATATTTATTATTATGTTGAATGTTAAATATAGTATCTATGTAG AAACAAAAAAAAAA

FIG. 71B

Met Tyr Arg Met Gin Leu Leu Ser Cys Ile Ala Leu Ile Leu Ala Leu Val Thr Asn Ser Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Lys Lys Thr Gin Leu Gin Leu Gin His Leu Leu Leu Asp Leu Gin Met Ile Leu Asn Giy Ile Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr Giu Leu Lys Gin Leu Gin Cys Leu Giu Glu Glu Glu Leu Lys Pro Leu Giu Glu Val Leu Asn Leu Ala Gin Ser Lys Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Giu Leu Lys Gily Ser Giu Thr Thr Phe Met Cys Giu Tyr Ala Asp Giu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Cys Gin Ser Ile Ile Ser Thr Leu Thr

FIG. 72A-1

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ATGCAAATAGAGCTCTCCACCTGCTTCTTTCTGTGCCTTTTGCGATTCT GCTTTAGTGCCACCAGAAGATACTACCTGGGTGCAGTGGAACTGTCA TGGGACTATATGCAAAGTGATCTCGGTGAGCTGCCTGTGGACGCAAG ATTTCCTCCTAGAGTGCCAAAATCTTTTCCATTCAACACCTCAGTCGT GTACAAAAAGACTCTGTTTGTAGAATTCACGGATCACCTTTTCAACAT CGCTAAGCCAAGGCCACCCTGGATGGGTCTGCTAGGTCCTACCATCC AGGCTGAGGTTTATGATACAGTGGTCATTACACTTAAGAACATGGCT TCCCATCCTGTCAGTCTTCATGCTGTTGGTGTATCCTACTGGAAAGCT TCTGAGGGAGCTGAATATGATGATCAGACCAGTCAAAGGGAGAAAG AAGATGATAAAGTCTTCCCTGGTGGAAGCCATACATATGTCTGGCAG GTCCTGAAAGAGAATGGTCCAATGGCCTCTGACCCACTGTGCCTTAC CTACTCATATCTTTCTCATGTGGACCTGGTAAAAGACTTGAATTCAGG CCTCATTGGAGCCCTACTAGTATGTAGAGAAGGGAGTCTGGCCAAGG AAAAGACACAGACCTTGCACAAATTTATACTACTTTTTGCTGTATTTG ATGAAGGGAAAAGTTGGCACTCAGAAACAAAGAACTCCTTGATGCA GGATAGGGATGCTGCATCTGCTCGGGCCTGGCCTAAAATGCACACAG TCAATGGTTATGTAAACAGGTCTCTGCCAGGTCTGATTGGATGCCACA GGAAATCAGTCTATTGGCATGTGATTGGAATGGGCACCACTCCTGAA GTGCACTCAATATTCCTCGAAGGTCACACATTTCTTGTGAGGAACCAT CGCCAGGCGTCCTTGGAAATCTCGCCAATAACTTTCCTTACTGCTCAA ACACTCTTGATGGACCTTGGACAGTTTCTACTGTTTTGTCATATCTCTT CCCACCAACATGATGGCATGGAAGCTTATGTCAAAGTAGACAGCTGT CCAGAGGAACCCCAACTACGAATGAAAAATAATGAAGAAGCGGAAG ACTATGATGATGATCTTACTGATTCTGAAATGGATGTGGTCAGGTTTG ATGATGACAACTCTCCTTCCTTTATCCAAATTCGCTCAGTTGCCAAGA AGCATCCTAAAACTTGGGTACATTACATTGCTGCTGAAGAGGAGGAC TGGGACTATGCTCCCTTAGTCCTCGCCCCGATGACAGAAGTTATAAA AGTCAATATTTGAACAATGGCCCTCAGCGGATTGGTAGGAAGTACAA AAAAGTCCGATTTATGGCATACACAGATGAAACCTTTAAGACTCGTG AAGCTATTCAGCATGAATCAGGAATCTTGGGACCTTTACTTTATGGGG TCAAGGAGATTACCAAAAGGTGTAAAACATTTGAAGGATTTTCCAAT TCTGCCAGGAGAAATATTCAAATATAAATGGACAGTGACTGTAGAAG ATGGGCCAACTAAATCAGATCCTCGGTGCCTGACCCGCTATTACTCTA GTTTCGTTAATATGGAGAGAGATCTAGCTTCAGGACTCATTGGCCCTC TCCTCATCTGCTACAAAGAATCTGTAGATCAAAGAGGAAACCAGATA ATGTCAGACAAGAGGAATGTCATCCTGTTTTCTGTATTTGATGAGAAC CGAAGCTGGTACCTCACAGAGAATATACAACGCTTTCTCCCCAATCCA GCTGGAGTGCAGCTTGAGGATCCAGAGTTCCAAGCCTCCAACATCAT GCACAGCATCAATGGCTATGTTTTTGATAGTTTGCAGTTGTCAGTTTG TTTGCATGAGGTGGCATACTGGTACATTCTAAGCATTGGAGCACAGA CTGACTTCCTTTCTCTCTCTCTGGATATACCTTCAAACACAAAAT

FIG. 72A-2 299/497

GGTCTATGAAGACACACTCACCCTATTCCCATTCTCAGGAGAAACTGT CTTCATGTCGATGGAAAACCCAGGTCTATGGATTCTGGGGTGCCACA ACTCAGACTTTCGGAACAGAGGCATGACCGCCTTACTGAAGGTTTCT AGTTGTGACAAGAACACTGGTGATTATTACGAGGACAGTTATGAAGA TATTTCAGCATACTTGCTGAGTAAAAACAATGCCATTGAACCAAGAA GCTTCTCCCAGAATTCAAGACACCGTAGCACTAGGCAAAAGCAATTT AATGCCACCACAATTCCAGAAAATGACATAGAGAAGACTGACCCTTG GTTTGCACACAGAACACCTATGCCTAAAATACAAAATGTCTCCTCTA GTGATTTGTTGATGCTCTTGCGACAGAGTCCTACTCCACATGGGCTAT CCTTATCTGATCTCCAAGAAGCCAAATATGAGACTTTTTCTGATGATC CATCACCTGGAGCAATAGACAGTAATAACAGCCTGTCTGAAATGACA CACTTCAGGCCACAGCTCCATCACAGTGGGGACATGGTATTTACCCC TGAGTCAGGCCTCCAATTAAGATTAAATGAGAAACTGGGGACAACTG CAGCAACAGAGTTGAAGAAACTTGATTTCAAAGTTTCTAGTACATCA AATAATCTGATTTCAACAATTCCATCAGACAATTTGGCAGCAGGTACT GATAATACAAGTTCCTTAGGACCCCCAAGTATGCCAGTTCATTATGAT AGTCAATTAGATACCACTCTATTTGGCAAAAAGTCATCTCCCCTTACT GAGTCTGGTGGACCTCTGAGCTTGAGTGAAGAAAATAATGATTCAAA GTTGTTAGAATCAGGTTTAATGAATAGCCAAGAAAGTTCATGGGGAA AAAATGTATCGTCAACAGAGAGTGGTAGGTTATTTAAAGGGAAAAGA GCTCATGGACCTGCTTTGTTGACTAAAGATAATGCCTTATTCAAAGTT AGCATCTCTTTGTTAAAGACAAACAAAACTTCCAATAATTCAGCAACT AATAGAAAGACTCACATTGATGGCCCATCATTATTAATTGAGAATAG TCCATCAGTCTGGCAAAATATATTAGAAAGTGACACTGAGTTTAAAA AAGTGACACCTTTGATTCATGACAGAATGCTTATGGACAAAAATGCT ACAGCTTTGAGGCTAAATCATATGTCAAATAAAACTACTTCATCAAA AAACATGGAAATGGTCCAACAGAAAAAAGAGGGCCCCATTCCACCA GATGCACAAAATCCAGATATGTCGTTCTTTAAGATGCTATTCTTGCCA GAATCAGCAAGGTGGATACAAAGGACTCATGGAAAGAACTCTCTGAA CTCTGGGCAAGGCCCCAGTCCAAAGCAATTAGTATCCTTAGGACCAG AAAAATCTGTGGAAGGTCAGAATTTCTTGTCTGAGAAAAACAAAGTG GTAGTAGGAAAGGGTGAATTTACAAAGGACGTAGGACTCAAAGAGA TGGTTTTTCCAAGCAGCAGAAACCTATTTCTTACTAACTTGGATAATT TACATGAAAATAATACACACAATCAAGAAAAAAAAATTCAGGAAGA AATAGAAAAGAAGGAAACATTAATCCAAGAGAATGTAGTTTTGCCTC AGATACATACAGTGACTGGCACTAAGAATTTCATGAAGAACCTTTTC TTACTGAGCACTAGGCAAAATGTAGAAGGTTCATATGACGGGGCATA TGCTCCAGTACTTCAAGATTTTAGGTCATTAAATGATTCAACAAATAG AACAAAGAAACACACAGCTCATTTCTCAAAAAAAGGGGAGGAAGAA AACTTGGAAGGCTTGGGAAATCAAACCAGCAAATTGTAGAGAAATAT GCATGCACCACAAGGAATATCTCCTAATACAAGCCAGCAGAATTTTG TCACGCAACGTAGTAAGAGAGCTTTGAAACAATTCAGACTCCCACTA

FIG. 72A-3 300/497

GAAGAACAGAACTTGAAAAAAGGATAATTGTGGATGACACCTCAAC CCAGTGGTCCAAAAACATGAAACATTTGACCCCGAGCACCCTCACAC AGATAGACTACAATGAGAAGGAGAAAGGGGCCATTACTCAGTCTCCC TTATCAGATTGCCTTACGAGGAGTCATAGCATCCCTCAAGCAAATAGA TCTCCATTACCCATTGCAAAGGTATCATCATTTCCATCTATTAGACCTA TATATCTGACCAGGGTCCTATTCCAAGACAACTCTTCTCATCTTCCAG CAGCATCTTATAGAAAGAAAGATTCTGGGGTCCAAGAAAGCAGTCAT TTCTTACAAGGAGCCAAAAAAAAAAAACCTTTCTTTAGCCATTCTAACC TTGGAGATGACTGGTGATCAAAGAGAGGTTGGCTCCCTGGGGACAAG TGCCACAAATTCAGTCACATACAAGAAAGTTGAGAACACTGTTCTCCC GAAACCAGACTTGCCCAAAACATCTGGCAAAGTTGAATTGCTTCCAA AAGTTCACATTTATCAGAAGGACCTATTCCCTACGGAAACTAGCAATG GGTCTCCTGGCCATCTGGATCTCGTGGAAGGGAGCCTTCTTCAGGGAA CAGAGGGAGCGATTAAGTGGAATGAAGCAAACAGACCTGGAAAAGT GCTATTGGATCCTCTTGCTTGGGATAACCACTATGGTACTCAGATACC AAAAGAAGAGTGGAAATCCCAAGAGAAGTCACCAGAAAAAAACAGCT TTTAAGAAAAAGGATACCATTTTGTCCCTGAACGCTTGTGAAAGCAAT CATGCAATAGCAGCAATAAATGAGGGACAAAATAAGCCCGAAATAG AAGTCACCTGGGCAAAGCAAGGTAGGACTGAAAGGCTGTGCTCTCAA AACCCACCAGTCTTGAAACGCCATCAACGGGAAATAACTCGTACTAC TCTTCAGTCAGATCAAGAGGAAATTGACTATGATGATACCATATCAGT TGAAATGAAGAAGGAAGATTTTGACATTTATGATGAGGATGAAAATC AGAGCCCCCGCAGCTTTCAAAAGAAAACACGACACTATTTTATTGCTG CAGTGGAGAGGCTCTGGGATTATGGGATGAGTAGCTCCCCACATGTT CTAAGAAACAGGGCTCAGAGTGGCAGTGTCCCTCAGTTCAAGAAAGT TGTTTTCCAGGAATTTACTGATGGCTCCTTTACTCAGCCCTTATACCGT GGAGAACTAAATGAACATTTGGGACTCCTGGGGCCATATATAAGAGC AGAAGTTGAAGATAATATCATGGTAACTTTCAGAAATCAGGCCTCTC GTCCCTATTCCTTCTATTCTAGCCTTATTTCTTATGAGGAAGATCAGAG GCAAGGAGCAGAACCTAGAAAAAACTTTGTCAAGCCTAATGAAACCA AAACTTACTTTTGGAAAGTGCAACATCATATGGCACCCACTAAAGAT GAGTTTGACTGCAAAGCCTGGGCTTATTTCTCTGATGTTGACCTGGAA AAAGATGTGCACTCAGGCCTGATTGGACCCCTTCTGGTCTGCCACACT AACACACTGAACCCTGCTCATGGGAGACAAGTGACAGTACAGGAATT TGCTCTGTTTTTCACCATCTTTGATGAGACCAAAAGCTGGTACTTCACT GAAAATATGGAAAGAAACTGCAGGGCTCCCTGCAATATCCAGATGGA CATAATGGATACACTACCTGGCTTAGTAATGGCTCAGGATCAAAGGA TTCGATGGTATCTGCTCAGCATGGGCAGCAATGAAAACATCCATTCT TAAAATGGCACTGTACAATCTCTATCCAGGTGTTTTTTGAGACAGTGGA

FIG. 72A-4

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AATGTTACCATCCAAAGCTGGAATTTGGCGGGTGGAATGCCTTATTGG CGAGCATCTACATGCTGGGATGAGCACACTTTTTCTGGTGTACAGCAA TAAGTGTCAGACTCCCCTGGGAATGGCTTCTGGACACATTAGAGATTT TCAGATTACAGCTTCAGGACAATATGGACAGTGGGCCCCAAAGCTGG CCAGACTTCATTATTCCGGATCAATCAATGCCTGGAGCACCAAGGAG CCCTTTTCTTGGATCAAGGTGGATCTGTTGGCACCAATGATTATTCAC GGCATCAAGACCCAGGGTGCCCGTCAGAAGTTCTCCAGCCTCTACAT CTCTCAGTTTATCATCATGTATAGTCTTGATGGGAAGAAGTGGCAGA CTTATCGAGGAAATTCCACTGGAACCTTAATGGTCTTCTTTGGCAATG TGGATTCATCTGGGATAAAACACAATATTTTTAACCCTCCAATTATTG CTCGATACATCCGTTTGCACCCAACTCATTATAGCATTCGCAGCACTC TTCGCATGGAGTTGATGGGCTGTGATTTAAATAGTTGCAGCATGCCAT TGGGAATGGAGAGTAAAGCAATATCAGATGCACAGATTACTGCTTCA TCCTACTTTACCAATATGTTTGCCACCTGGTCTCCTTCAAAAGCTCGA CTTCACCTCCAAGGGAGGAGTAATGCCTGGAGACCTCAGGTGAATAA TCCAAAAGAGTGGCTGCAAGTGGACTTCCAGAAGACAATGAAAGTCA CAGGAGTAACTACTCAGGGAGTAAAATCTCTGCTTACCAGCATGTAT GTGAAGGAGTTCCTCATCTCCAGCAGTCAAGATGGCCATCAGTGGAC TCTCTTTTTCAGAATGGCAAAGTAAAGGTTTTTCAGGGAAATCAAGA CTCCTTCACACCTGTGGTGAACTCTCTAGACCCACCGTTACTGACTCG CTACCTTCGAATTCACCCCCAGAGTTGGGTGCACCAGATTGCCCTGAG GATGGAGGTTCTGGGCTGCGAGGCACAGGACCTCTACTGAGGGTGGC CACTGCAGCACCTGCCACTGCCGTCACCTCTCCCTCCAGCTCCAGG GCAGTGTCCCTCCCTGGCTTGCCTTCTACCTTTGTGCTAAATCCTAGC AGACACTGCCTTGAAGCCTCCTGAATTAACTATCATCAGTCCTGCATT TCTTTGGTGGGGGCCAGGAGGGTGCATCCAATTTAACTTAACTCTTA AGGCAAAAAGAAGTGAGGAGAAACCTGCATGAAAGCATTCTTCCCTG AAAAGTTAGGCCTCTCAGAGTCACCACTTCCTCTGTTGTAGAAAAACT ATGTGATGAAAACTTTGAAAAAGATATTTATGATGTTAACATTTCAGGT TAAGCCTCATACGTTTAAAATAAAACTCTCAGTTGTTTATTATCCTGA TCAAGCATGGAACAAAGCATGTTTCAGGATCAGATCAATACAATCTT GGAGTCAAAAGGCAAATCATTTGGACAATCTGCAAAATGGAGAGAA TACAATAACTACTACAGTAAAGTCTGTTTCTGCTTCCTTACACATAGA TATAATTATGTTATTTAGTCATTATGAGGGGCACATTCTTATCTCCAA AACTAGCATTCTTAAACTGAGAATTATAGATGGGGTTCAAGAATCCC TAAGTCCCCTGAAATTATATAAGGCATTCTGTATAAATGCAAATGTGC ATTTTTCTGACGAGTGTCCATAGATATAAAGCCATTTGGTCTTAATTCT GACCAATAAAAAAATAAGTCAGGAGGATGCAATTGTTGAAAGCTTTG AAATGATGA

FIG. 72B-1

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Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe Cys Phe Ser Ala Thr Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser Trp Asp Tyr Met Gln Ser Asp Leu Gly Glu Leu Pro Val Asp Ala Arg Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln Ala Glu Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp Asp Lys Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu Lys Glu Asn Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile Phe Leu Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met Asp Leu Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asp Ser Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu Leu Ile Ile Phe Lys Asp Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu Ser Val Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val Ile Leu Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp Pro Glu Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val Phe Asp Ser Leu Gin Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe Ser Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe

FIG. 72B-2

Arg Asn Arg Gly Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Ser Arg His Arg Ser Thr Arg Gln Lys Gln Phe Asn Ala Thr Thr Ile Pro Glu Asn Asp Ile Glu Lys Thr Asp Pro Trp Phe Ala His Arg Thr Pro Met Pro Lys Ile Gln Asn Val Ser Ser Ser Asp Leu Leu Met Leu Leu Arg Gin Ser Pro Thr Pro His Gly Leu Ser Leu Ser Asp Leu Gin Glu Ala Lys Tyr Giu Thr Phe Ser Asp Asp Pro Ser Pro Gly Ala Ile Asp Ser Asn Asn Ser Leu Ser Glu Met Thr His Phe Arg Pro Gln Leu His His Ser Gly Asp Met Val Phe Thr Pro Glu Ser Gly Leu Gln Leu Arg Leu Asn Glu Lys Leu Gly Thr Thr Ala Ala Thr Glu Leu Lys Lys Leu Asp Phe Lys Val Ser Ser Thr Ser Asn Asn Leu lle Ser Thr Ile Pro Ser Asp Asn Leu Ala Ala Gly Thr Asp Asn Thr Ser Ser Leu Gly Pro Pro Ser Met Pro Val His Tyr Asp Ser Gln Leu Asp Thr Thr Leu Phe Gly Lys Lys Ser Ser Pro Leu Thr Glu Ser Gly Gly Pro Leu Ser Leu Ser Glu Glu Asn Asn Asp Ser Lys Leu Clu Ser Gly Leu Met Asn Ser Gln Glu Ser Ser Trp Gly Lys Asn Val Ser Ser Thr Glu Ser Gly Arg Leu Phe Lys Gly Lys Arg Ala His Gly Pro Ala Leu Leu Thr Lys Asp Asn Ala Leu Phe Lys Val Ser Ile Ser Leu Leu Lys Thr Asn Lys Thr Ser Asn Asn Ser Ala Thr Asn Arg Lys Thr His Ile Asp Gly Pro Ser Leu Leu Ile Glu Asn Ser Pro Ser Val Trp Gln Asn Ile Leu Glu Ser Asp Thr Glu Phe Lys Lys Val Thr Pro Leu Ile His Asp Arg Met Leu Met Asp Lys Asn Ala Thr Ala Leu Arg Leu Asn His Met Ser Asn Lys Thr Thr Ser Ser Lys Asn Met Glu Met Val Gln Gln Lys Lys Glu Gly Pro Ile Pro Pro Asp Ala Gln Asn Pro Asp Met Ser Phe Phe Lys Met Leu Phe Leu Pro Glu Ser Ala Arg Trp Ile Gln Arg Thr His Gly Lys Asn Ser Leu Asn Ser Gly Gln Gly Pro Ser Pro Lys Gin Leu Val Ser Leu Gly Pro Glu Lys Ser Val Glu Gly Gin Asn Phe Leu Ser Glu Lys Asn Lys Val Val Val Gly Lys Gly Glu Phe Thr Lys Asp Val Gly Leu Lys Glu Met Val Phe Pro Ser Ser Arg Asn Leu Phe Leu Thr Asn Leu Asp Asn Leu His Glu Asn Asn Thr His Asn Gln Glu Lys Lys Ile Gln Glu Glu Ile Glu Lys Lys Glu Thr Leu Ile Gln Glu Asn Val Val Leu Pro Gln Ile His Thr Val Thr Gly Thr Lys Asn Phe Met Lys Asn Leu Phe Leu Leu Ser Thr Arg Gln Asn Val Glu Gly Ser Tyr Asp Gly Ala Tyr Ala Pro Val Leu Gln Asp Phe Arg Ser Leu Asn Asp Ser Thr Asn Arg Thr Lys Lys His Thr Ala His Phe Ser Lys Lys Gly Glu Glu Asn Leu Glu Gly Leu Gly Asn Gln Thr Lys Gln Ile Val Glu Lys Tyr Ala Cys Thr Thr Arg Ile Ser Pro Asn Thr Ser Gln Gln Asn Phe Val Thr Gln Arg Ser Lys Arg Ala Leu Lys Gln Phe Arg Leu Pro Leu Glu Glu Thr Glu Leu Glu Lys Arg Ile Ile Val Asp Asp Thr Ser Thr Gln Trp Ser Lys Asn Met Lys His Leu Thr Pro Ser Thr Leu Thr Gln Ile Asp Tyr Asn Glu Lys Glu Lys Gly Ala Ile Thr Gln Ser Pro Leu Ser Asp Cys Leu Thr Arg Ser His Ser Ile Pro Gln Ala Asn Arg Ser Pro Leu Pro Ile Ala Lys Val Ser Ser Phe Pro Ser Ile Arg Pro Ile Tyr Leu Thr Arg Val Leu Phe Gln Asp Asn Ser Ser His Leu Pro

FIG. 72B-3

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Ala Ala Ser Tyr Arg Lys Lys Asp Ser Gly Val Gln Glu Ser Ser His Phe Leu Gln Gly Ala Lys Lys Asn Asn Leu Ser Leu Ala Ile Leu Thr Leu Glu Met Thr Gly Asp Gln Arg Glu Val Gly Ser Leu Gly Thr Ser Ala Thr Asn Ser Val Thr Tyr Lys Lys Val Glu Asn Thr Val Leu Pro Lys Pro Asp Leu Pro Lys Thr Ser Gly Lys Val Glu Leu Leu Pro Lys Val His Ile Tyr Gln Lys Asp Leu Phe Pro Thr Glu Thr Ser Asn Gly Ser Pro Gly His Leu Asp Leu Val Glu Gly Ser Leu Leu Gln Gly Thr Glu Gly Ala Ile Lys Trp Asn Glu Ala Asn Arg Pro Gly Lys Val Pro Phe Leu Arg Val Ala Thr Glu Ser Ser Ala Lys Thr Pro Ser Lys Leu Leu Asp Pro Leu Ala Trp Asp Asn His Tyr Gly Thr Gln Ile Pro Lys Glu Glu Trp Lys Ser Gln Glu Lys Ser Pro Glu Lys Thr Ala Phe Lys Lys Lys Asp Thr Ile Leu Ser Leu Asn Ala Cys Glu Ser Asn His Ala Ile Ala Ala Ile Asn Glu Gly Gln Asn Lys Pro Glu Ile Glu Val Thr Trp Ala Lys Gln Gly Arg Thr Glu Arg Leu Cys Ser Gln Asn Pro Pro Val Leu Lys Arg His Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser Val Pro Gin Phe Lys Lys Val Val Phe Gin Glu Phe Thr Asp Gly Ser Phe Thr Gin Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly Pro Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala Pro Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr Arg Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly Leu Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr Leu Leu Ser Met Glv Ser Asn Glu Asn Ile His Ser Ile His Phe Ser Gly His Val Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met Ala Leu Tyr Asn Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met Leu Pro Ser Lys Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly Glu His Leu His Ala Gly Met Ser Thr Leu Phe Leu Val Tyr Ser Asn Lys Cys Gln Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg Asp Phe Gin Ile Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala Arg Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Glu Pro Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile His Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu Tyr Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys Trp Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe Phe Gly Asn Val Asp Ser Ser Gly Ile

FIG. 72B-4

Lys His Asn Ile Phe Asn Pro Pro Ile Ile Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr Ser Ile Arg Ser Thr Leu Arg Met Glu Leu Met Gly Cys Asp Leu Asn Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys Ala Ile Ser Asp Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr Trp Ser Pro Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser Asn Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu Trp Leu Gln Val Asp Phe Gln Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln Gly Val Lys Ser Leu Leu Thr Ser Met Tyr Val Lys Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu Phe Phe Gln Asn Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr Pro Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr Arg Tyr Leu Arg Ile His Pro Gln Ser Trp Val His Gln Ile Ala Leu Arg Met Glu Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr

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FIG. 73A

TCCACCTGTCCCCGCAGCGCCGGCTCGCGCCCTCCTGCCGCAGCCACC GAGCCGCCGTCTAGCGCCCCGACCTCGCCACCATGAGAGCCCTGCTG GCGCGCCTGCTTCTCTGCGTCCTGGTCGTGAGCGACTCCAAAGGCAGC A ATGAACTTCATCAAGTTCCATCGAACTGTGACTGTCTAAATGGAGGA ACATGTGTGTCCAACAAGTACTTCTCCAACATTCACTGGTGCAACTGC CCAAAGAAATTCGGAGGGCAGCACTGTGAAATAGATAAGTCAAAAAC CTGCTATGAGGGGAATGGTCACTTTTACCGAGGAAAGGCCAGCACTG ACACCATGGGCCGGCCCTGCCTGCCCTGGAACTCTGCCACTGTCCTTC AGCAAACGTACCATGCCCACAGATCTGATGCTCTTCAGCTGGGCCTGG GGAAACATAATTACTGCAGGAACCCAGACAACCGGAGGCGACCCTGG TGCTATGTGCAGGTGGGCCTAAAGCCGCTTGTCCAAGAGTGCATGGT GCATGACTGCGCAGATGGAAAAAAGCCCTCCTCTCCCAGAAGAAT TAAAATTTCAGTGTGGCCAAAAGACTCTGAGGCCCCGCTTTAAGATTA TTGGGGGAGAATTCACCACCATCGAGAACCAGCCCTGGTTTGCGGCC ATCTACAGGAGGCACCGGGGGGGCTCTGTCACCTACGTGTGTGGAGG CAGCCTCATCAGCCCTTGCTGGGTGATCAGCGCCACACACTGCTTCAT TGATTACCCAAAGAAGGAGGACTACATCGTCTACCTGGGTCGCTCAA GGCTTAACTCCAACACGCAAGGGGAGATGAAGTTTGAGGTGGAAAAC CTCATCCTACACAAGGACTACAGCGCTGACACGCTTGCTCACCACAAC GACATTGCCTTGCTGAAGATCCGTTCCAAGGAGGGCAGGTGTGCGCA GCCATCCCGGACTATACAGACCATCTGCCTGCCTCGATGTATAACGA TCCCCAGTTTGGCACAAGCTGTGAGATCACTGGCTTTGGAAAAGAGA ATTCTACCGACTATCTCTATCCGGAGCAGCTGAAGATGACTGTTGTGA AGCTGATTTCCCACCGGGAGTGTCAGCAGCCCCACTACTACGGCTCTG A A GTC A CCACCA A A A TGCTGTGTGTGCTGCTGACCCACAGTGGAAAACA GATTCCTGCCAGGGAGACTCAGGGGGACCCCTCGTCTGTTCCCTCCAA GGCCGCATGACTTTGACTGGAATTGTGAGCTGGGGCCGTGGATGTGC CCTGAAGGACAAGCCAGGCGTCTACACGAGAGTCTCACACTTCTTAC CCTGGATCCGCAGTCACCCAAGGAAGAGAATGGCCTGGCCCTCTGA GGGTCCCCAGGGAGGAAACGGGCACCACCCGCTTTCTTGCTGGTTGTC ATTTTTGCAGTAGAGTCATCTCCATCAGCTGTAAGAAGAGACTGGGA AGAT

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FIG. 73B

Met Arg Ala Leu Leu Ala Arg Leu Leu Leu Cys Val Leu Val Val Ser Asp Ser Lys Gly Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr Asp Thr Met Gly Arg Pro Cys Leu Pro Tro Asn Ser Ala Thr Val Leu Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Phe Ala Ala Ile Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Leu Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Ile Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr Thr Lys Met Leu Cys Ala Ala Asp Pro Gin Trp Lys Thr Asp Ser Cys Gin Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu

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FIG.74A

TCCTGCACAGGCAGTGCCTTGAAGTGCTTCTTCAGAGACCTTTCTTCA TAGACTACTTTTTTTTTTTAAGCAGCAAAAGGAGAAAATTGTCATCA AGGATATTCCAGATTCTTGACAGCATTCTCGTCATCTCTGAGGACATC ACCATCATCTCAGGATGAGGGGCATGAAGCTGCTGGGGGGCGCTGCTG GCACTGGCGGCCCTACTGCAGGGGGCCGTGTCCCTGAAGATCGCAGC CTTCAACATCCAGACATTTGGGGAGACCAAGATGTCCAATGCCACCCT CGTCAGCTACATTGTGCAGATCCTGAGCCGCTATGACATCGCCCTGGT CCAGGAGGTCAGAGACAGCCACCTGACTGCCGTGGGGAAGCTGCTGG ACAACCTCAATCAGGATGCACCAGACACCTATCACTACGTGGTCAGT GAGCCACTGGGACGGAACAGCTATAAGGAGCGCTACCTGTTCGTGTA CAGGCCTGACCAGGTGTCTGCGGTGGACAGCTACTACTACGATGATG GTCAGGTTCTTCTCCCGGTTCACAGAGGTCAGGGAGTTTGCCATTGTT CCCCTGCATGCGGCCCCGGGGGACGCAGTAGCCGAGATCGACGCTCT CTATGACGTCTACCTGGATGTCCAAGAGAAATGGGGCTTGGAGGACG TCATGTTGATGGGCGACTTCAATGCGGGCTGCAGCTATGTGAGACCCT CCCAGTGGTCATCCATCCGCCTGTGGACAAGCCCCACCTTCCAGTGGC TGATCCCCGACAGCGCTGACACCACAGCTACACCCACGCACTGTGCCT ATGACAGGATCGTGGTTGCAGGGATGCTGCTCCGAGGCGCCGTTGTTC CCGACTCGGCTCTTCCCTTTAACTTCCAGGCTGCCTATGGCCTGAGTG ACCAACTGGCCCAAGCCATCAGTGACCACTATCCAGTGGAGGTGATG CTGAAGTGAGCAGCCCCTCCCCACACCAGTTGAACTGCAG

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FIG. 74B

Met Arg Gly Met Lys Leu Leu Gly Ala Leu Leu Ala Leu Ala Ala Leu Leu Gln Gly Ala Val Ser Leu Lys Ile Ala Ala Phe Asn Ile Gin Thr Phe Gly Glu Thr Lys Met Ser Asn Ala Thr Leu Val Ser Tyr Ile Val Gln Ile Leu Ser Arg Tyr Asp Ile Ala Leu Val Gin Glu Val Arg Asp Ser His Leu Thr Ala Val Gly Lys Leu Leu Asp Asn Leu Asn Gln Asp Ala Pro Asp Thr Tyr His Tyr Val Val Ser Glu Pro Leu Gly Arg Asn Ser Tyr Lys Glu Arg Tyr Leu Phe Val Tyr Arg Pro Asp Gln Val Ser Ala Val Asp Ser Tyr Tyr Tyr Asp Asp Gly Cys Glu Pro Cys Gly Asn Asp Thr Phe Asn Arg Glu Pro Ala Ile Val Arg Phe Phe Ser Arg Phe Thr Glu Val Arg Glu Phe Ala Ile Val Pro Leu His Ala Ala Pro Gly Asp Ala Val Ala Glu Ile Asp Ala Leu Tyr Asp Val Tyr Leu Asp Val Gin Giu Lys Trp Gly Leu Glu Asp Val Met Leu Met Gly Asp Phe Asn Ala Gly Cys Ser Tyr Val Arg Pro Ser Gln Trp Ser Ser Ile Arg Leu Trp Thr Ser Pro Thr Phe Gln Trp Leu Ile Pro Asp Ser Ala Asp Thr Thr Ala Thr Pro Thr His Cys Ala Tyr Asp Arg Ile Val Val Ala Gly Met Leu Leu Arg Gly Ala Val Val Pro Asp Ser Ala Leu Pro Phe Asn Phe Gln Ala Ala Tyr Gly Leu Ser Asp Gln Leu Ala Gln Ala Ile Ser Asp His Tyr Pro Val Glu Val Met Leu Lys

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FIG. 75A

FIG. 75B

Met Ala Leu Trp Met Arg Leu Leu Pro Leu Leu Ala Leu Leu Ala Leu Trp Gly Pro Asp Pro Ala Ala Ala Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Arg Arg Glu Ala Glu Asp Leu Gln Val Gly Gin Val Glu Leu Gly Gly Gly Pro Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln Lys Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn

FIG. 76A

ATGGGAGGTTGGTCTTCCAAACCTCGACAAGGCATGGGGACGAATCT TTCTGTTCCCAATCCTCTGGGATTCTTTCCCGATCACCAGTTGGACCCT GCGTTCGGAGCCAACTCAAACAATCCAGATTGGGACTTCAACCCCAA CAAGGATCACTGGCCAGAGGCAATCAAGGTAGGAGCGGGAGACTTC GGGCCAGGGTTCACCCCACCACACGGCGGTCTTTTGGGGTGGAGCCC TCAGGCTCAGGGCATATTGACAACAGTGCCAGCAGCGCCTCCTCCTG TTTCCACCAATCGGCAGTCAGGAAGACAGCCTACTCCCATCTCTCCAC CTCTAAGAGACAGTCATCCTCAGGCCATGCAGTGGAACTCCACAACA TTCCACCAAGCTCTGCTAGATCCCAGAGTGAGGGGCCTATATTTTCCT GCTGGTGGCTCCAGTTCCGGAACAGTAAACCCTGTTCCGACTACTGTC TCACCCATATCGTCAATCTTCTCGAGGACTGGGGACCCTGCACCGAAC ATGGAGAGCACAACATCAGGATTCCTAGGACCCCTGCTCGTGTTACA GGCGGGGTTTTTCTTGTTGACAAGAATCCTCACAATACCACAGAGTCT AGACTCGTGGTGGACTTCTCTCAATTTTCTAGGGGGAGCACCCACGTG TTGTCCTCCAATTTGTCCTGGTTATCGCTGGATGTCTCTGCGGCGTTTT ATCATATTCCTCTTCATCCTGCTGCTATGCCTCATCTTCTTGTTGGTTC TTCTGGACTACCAAGGTATGTTGCCCGTTTGTCCTCTACTTCCAGGAA CATCAACTACCAGCACGGGACCATGCAAGACCTGCACGATTCCTGCT CAAGGAACCTCTATGTTTCCCTCTTGTTGCTGTACAAAACCTTCGGAC GGAAACTGCACTTGTATTCCCATCCCATCATCCTGGGCTTTCGCAAGA TTCCTATGGGAGTGGGCCTCAGTCCGTTTCTCCTGGCTCAGTTTACTA GTGCCATTTGTTCAGTGGTTCGCAGGGCTTTCCCCCACTGTTTGGCTTT CAGTTATATGGATGATGTGGTATTGGGGGCCAAGTCTGTACAACATCT TGAGTCCCTTTTTACCTCTATTACCAATTTTCTTTTGTCTTTGGGTATAC ATTTGA

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FIG. 76B

Met Gly Gly Trp Ser Ser Lys Pro Arg Gln Gly Met Gly Thr Asn Leu Ser Val Pro Asn Pro Leu Gly Phe Phe Pro Asp His Gln Leu Asp Pro Ala Phe Gly Ala Asn Ser Asn Asn Pro Asp Trp Asp Phe Asn Pro Asn Lys Asp His Trp Pro Glu Ala Ile Lys Val Gly Ala Gly Asp Phe Gly Pro Gly Phe Thr Pro Pro His Gly Gly Leu Leu Gly Trp Ser Pro Gln Ala Gln Gly Ile Leu Thr Thr Val Pro Ala Ala Pro Pro Pro Val Ser Thr Asn Arg Gln Ser Gly Arg Gln Pro Thr Pro Ile Ser Pro Pro Leu Arg Asp Ser His Pro Gln Ala Met Gln Trp Asn Ser Thr Thr Phe His Gln Ala Leu Leu Asp Pro Arg Val Arg Gly Leu Tyr Phe Pro Ala Gly Gly Ser Ser Ser Gly Thr Val Asn Pro Val Pro Thr Thr Val Ser Pro Ile Ser Ser Ile Phe Ser Arg Thr Gly Asp Pro Ala Pro Asn Met Glu Ser Thr Thr Ser Gly Phe Leu Gly Pro Leu Leu Val Leu Gln Ala Gly Phe Phe Leu Leu Thr Arg Ile Leu Thr Ile Pro Gln Ser Leu Asp Ser Tro Tro Thr Ser Leu Asn Phe Leu Gly Gly Ala Pro Thr Cys Pro Gly Gln Asn Ser Gln Ser Pro Thr Ser Asn His Ser Pro Thr Ser Cys Pro Pro Ile Cys Pro Gly Tyr Arg Trp Met Cys Leu Arg Arg Phe Ile Ile Phe Leu Phe Ile Leu Leu Leu Cys Leu Ile Phe Leu Leu Val Leu Leu Asp Tyr Gln Gly Met Leu Pro Val Cys Pro Leu Leu Pro Gly Thr Ser Thr Thr Ser Thr Gly Pro Cys Lys Thr Cys Thr Ile Pro Ala Gln Gly Thr Ser Met Phe Pro Ser Cys Cys Cys Thr Lys Pro Ser Asp Gly Asn Cys Thr Cys Ile Pro Ile Pro Ser Ser Trp Ala Phe Ala Arg Phe Leu Trp Glu Trp Ala Ser Val Arg Phe Ser Trp Leu Ser Leu Leu Val Pro Phe Val Gln Trp Phe Ala Gly Leu Ser Pro Thr Val Trp Leu Ser Val Ile Trp Met Met Trp Tyr Trp Gly Pro Ser Leu Tyr Asn Ile Leu Ser Pro Phe Leu Pro Leu Leu Pro Ile Phe Phe Cys Leu Trp Val Tyr Ile

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FIG. 77A

CGAACCACTCAGGGTCCTGTGGACAGCTCACCTAGCTGCAATGGCTA CCTGGCTTCAAGAGGGCAGTGCCTTCCCAACCATTCCCTTATCCAGGC CTTTTGACAACGCTATGCTCCGCGCCCATCGTCTGCACCAGCTGGCCT TTGACACCTACCAGGAGTTTGAAGAAGCCTATATCCCAAAGGAACAG AAGTATTCATTCCTGCAGAACCCCCAGACCTCCCTCTGTTTCTCAGAG TCTATTCCGACACCCTCCAACAGGGAGGAAACACAACAGAAATCCAA CCTAGAGCTGCTCCGCATCTCCCTGCTGCTCATCCAGTCGTGGCTGGA GCCCGTGCAGTTCCTCAGGAGTGTCTTCGCCAACAGCCTGGTGTACGG CGCCTCTGACAGCAACGTCTATGACCTCCTAAAGGACCTAGAGGAAG GCATCCAAACGCTGATGGGGAGGCTGGAAGATGGCAGCCCCCGGACT GGGCAGATCTTCAAGCAGACCTACAGCAAGTTCGACACAAACTCACA CAACGATGACGCACTACTCAAGAACTACGGGCTGCTCTACTGCTTCAG GAAGGACATGGCAAGGTCGAGACATTCCTGCGCATCGTGCAGTGCCG CTCTGTGGAGGGCAGCTGTGGCTTCTAGCTGCCCGGGTGGCATCCCTG TGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTTGCCACTCCAGT GCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATC

FIG. 77B

Met Ala Thr Gly Ser Arg Thr Ser Leu Leu Leu Ala Phe Gly Leu Leu Cys Leu Pro Trp Leu Gln Glu Gly Ser Ala Phe Pro Thr Ile Pro Leu Ser Arg Pro Phe Asp Asn Ala Met Leu Arg Ala His Arg Leu His Gln Leu Ala Phe Asp Thr Tyr Gln Glu Phe Glu Glu Ala Tyr Ile Pro Lys Glu Gln Lys Tyr Ser Phe Leu Gln Asn Pro Gln Thr Ser Leu Cys Phe Ser Glu Ser Ile Pro Thr Pro Ser Asn Arg Glu Glu Thr Gln Gln Lys Ser Asn Leu Glu Leu Leu Arg Ile Ser Leu Leu Leu Ile Gln Ser Trp Leu Gln Pro Val Gln Phe Leu Arg Ser Val Phe Ala Asn Ser Leu Val Tyr Gly Ala Ser Asp Ser Asn Val Tyr Asp Leu Leu Lys Asp Leu Glu Glu Gly Ile Gln Thr Leu Met Gly Arg Leu Glu Asp Gly Ser Pro Arg Thr Gly Gln Ile Phe Lys Gln Thr Tyr Ser Lys Phe Asp Thr Asn Ser His Asn Asp Asp Ala Leu Leu Lys Asn Tyr Gly Leu Leu Tyr Cys Phe Arg Lys Asp Met Asp Lys Val Glu Thr Phe Leu Arg Ile Val Gln CysArg Ser Val Glu Gly Ser Cys Gly Phe

FIG. 78A

TTATCTTTTGTCCTTGCTGCTCATTGGCTTCTGGGACTGCGTGACCTGT CACGGGAGCCCTGTGGACATCTGCACAGCCAAGCCGCGGGACATTCC CATGAATCCCATGTGCATTTACCGCTCCCCGGAGAAGAAGGCAACTG AGGATGAGGGCTCAGAACAGAAGATCCCGGAGGCCACCAACCGGCG TGTCTGGGAACTGTCCAAGGCCAATTCCCGCTTTGCTACCACTTTCTA TCAGCACCTGGCAGATTCCAAGAATGACAATGATAACATTTTCCTGTC ACCCCTGAGTATCTCCACGGCTTTTGCTATGACCAAGCTGGGTGCCTG TAATGACACCCTCCAGCAACTGATGGAGGTATTTAAGTTTGACACCAT ATCTGAGAAAACATCTGATCAGATCCACTTCTTTTTGCCAAACTGAA CTGCCGACTCTATCGAAAAGCCAACAAATCCTCCAAGTTAGTATCAGC CAATCGCCTTTTTGGAGACAAATCCCTTACCTTCAATGAGACCTACCA GGACATCAGTGAGTTGGTATATGGAGCCAAGCTCCAGCCCCTGGACT TCAAGGAAAATGCAGAGCAATCCAGAGCGGCCATCAACAAATGGGTG TCCAATAAGACCGAAGGCCGAATCACCGATGTCATTCCCTCGGAAGC CATCAATGAGCTCACTGTTCTGGTGCTGGTTAACACCATTTACTTCAA TGTTCTACAAGGCTGATGGAGAGTCGTGTTCAGCATCTATGATGTACC AGGAAGGCAAGTTCCGTTATCGGCGCGTGGCTGAAGGCACCCAGGTG CTTGAGTTGCCCTTCAAAGGTGATGACATCACCATGGTCCTCATCTTG CCCAAGCCTGAGAAGAGCCTGGCCAAGGTGGAGAAGGAACTCACCCC AGAGGTGCTGCAGGAGTGGCTGGATGAATTGGAGGAGATGATGCTGG TGGTCCACATGCCCCGCTTCCGCATTGAGGACGGCTTCAGTTTGAAGG AGCAGCTGCAAGACATGGGCCTTGTCGATCTGTTCAGCCCTGAAAAG TCCAAACTCCCAGGTATTGTTGCAGAAGGCCGAGATGACCTCTATGTC TCAGATGCATTCCATAAGGCATTTCTTGAGGTAAATGAAGAAGGCAG TGAAGCAGCTGCAAGTACCGCTGTTGTGATTGCTGGCCGTTCGCTAAA CCCCAACAGGGTGACTTTCAAGGCCAACAGGCCTTTCCTGGTTTTTAT AAGAGAAGTTCCTCTGAACACTATTATCTTCATGGGCAGAGTAGCCA ACCCTTGTGTTAAGTAA

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FIG. 78B

Met Tyr Ser Asn Val Ile Gly Thr Val Thr Ser Gly Lys Arg Lys Val Tyr Leu Leu Ser Leu Leu Leu Ile Gly Phe Trp Asp Cys Val Thr Cys His Gly Ser Pro Val Asp He Cvs Thr Ala Lvs Pro Arg Asp He Pro Met Asn Pro Met Cys He Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn Asp Thr Leu Gln Gln Leu Met Glu Val Phe Lys Phe Asp Thr Ile Ser Glu Lys Thr Ser Asp Gln Ile His Phe Phe Phe Ala Lys Leu Asn Cys Arg Leu Tyr Arg Lys Ala Asn Lys Ser Ser Lys Leu Val Ser Ala Asn Arg Leu Phe Gly Asp Lys Ser Leu Thr Phe Asn Glu Thr Tyr Gln Asp Ile Ser Glu Leu Val Tyr Gly Ala Lys Leu Gln Pro Leu Asp Phe Lys Glu Asn Ala Glu Gln Ser Arg Ala Ala Ile Asn Lys Trp Val Ser Asn Lys Thr Giu Gly Arg Ile Thr Asp Val Ile Pro Ser Glu Ala Ile Asn Glu Leu Thr Val Leu Val Leu Val Asn Thr Ile Tyr Phe Lys Gly Leu Trp Lys Ser Lys Phe Ser Pro Glu Asn Thr Arg Lys Glu Leu Phe Tyr Lys Ala Asp Gly Glu Ser Cys Ser Ala Ser Met Met Tyr Gln Glu Gly Lys Phe Arg Tyr Arg Arg Val Ala Glu Gly Thr Gln Val Leu Glu Leu Pro Phe Lys Gly Asp Asp Ile Thr Met Val Leu Ile Leu Pro Lys Pro Glu Lys Ser Leu Ala Lys Val Glu Lys Glu Leu Thr Pro Glu Val Leu Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala Ser Thr Ala Val Val Ile Ala Gly Arg Ser Leu Asn Pro Asn Arg Val Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro Leu Asn Thr He He Phe Met Glv Arg Val Ala Asn Pro Cys Val Lys

FIG. 79A

ATGGATTACTACAGAAAATATGCAGCTATCTTTCTGGTCACATTGTCG
GTGTTTCTGCATGTTCCATTCCGCTCCTGATGTCCAGGATTGCCCAG
AATGCACGCTACAGGAAAACCCCATTCTTCTCCCAGCCGGGTGCCCCA
ATACTTCAGTGCATGGGCTGCTTCTCTCTAGAGCATATCCCACTCCA
CTAAGGTCCAAGAAGACGATGTTGGTCCAAAAGAACGTCACCTCAGA
GTCCACTTGCTGTGTAGCTAAATCATATAACAGGGTCACAGTAATGGG
GGGTTTCAAAGTGGAGAACCACACGGCGTGCCACTGCAGTACTTGTT
ATTATCACAAAATCTTAA

FIG. 79B

Met Asp Tyr Tyr Arg Lys Tyr Ala Ala Ile Phe Leu Val Thr Leu Ser Val Phe Leu His Val Leu His Ser Ala Pro Asp Val Gin Asp Cys Pro Giu Cys Thr Leu Gin Giu Asn Pro Phe Phe Ser Gin Pro Giy Ala Pro Ile Leu Gin Cys Met Giy Cys Cys Phe Ser Arg Ala Tyr Pro Thr Pro Leu Arg Ser Lys Lys Thr Met Leu Val Gin Lys Asn Val Thr Ser Giu Ser Thr Cys Cys Val Ala Lys Ser Tyr Asn Arg Val Thr Val Met Giy Giy Phe Lys Val Giu Asn His Thr Ala Cys His Cys Ser Thr Cys Tyr Tyr His Lys Ser

FIG. 79C

FIG. 79D

Met Glu Met Phe Gln Gly Leu Leu Leu Leu Leu Leu Leu Ser Met Gly Gly Thr Trp Ala Ser Lys Glu Fro Leu Arg Pro Arg Cys Arg Pro Ile Asn Ala Thr Leu Ala Val Glu Lys Glu Gly Cys Pro Val Cys Ile Thr Val Asn Thr Thr Ile Cys Ala Gly Tyr Cys Pro Thr Met Thr Arg Val Leu Gln Gly Val Leu Pro Ala Leu Pro Gln Val Val Cys Asn Tyr Arg Asp Val Arg Phe Glu Ser Ile Arg Leu Pro Gly Cys Pro Arg Gly Val Asn Pro Val Val Ser Tyr Ala Val Ala Leu Ser Cys Gln Cys Ala Leu Cys Arg Arg Ser Thr Thr Asp Cys Gly Gly Pro Lys Asp His Pro Leu Thr Cys Asp Asp Pro Arg Phe Gln Asp Ser Ser Ser Ser Lys Ala Pro Pro Pro Ser Leu Pro Ser Pro Ser Arg Leu Pro Gly Pro Ser Asp Thr Pro Ile Leu Pro Gln

FIG. 80A

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ATGCGTCCCCTGCGCCCCCGCGCCGCGCTGCTGGCCTCCTGGCCTCG CTCCTGGCCGCGCCCCGGTGGCCCCGGCCGAGGCCCCGCACCTGGT GCAGGTGGACGCGCCCCGCGCGCTGTGGCCCCTGCGGCGCTTCTGGA GGAGCACAGGCTTCTGCCCCCCGCTGCCACACAGCCAGGCTGACCAG TACGTCCTCAGCTGGGACCAGCAGCTCAACCTCGCCTATGTGGGCGCC GTCCCTCACCGCGCATCAAGCAGGTCCGGACCCACTGGCTGCTGGA GCTTGTCACCACCAGGGGGTCCACTGGACGGGCCTGAGCTACAACT TCACCCACCTGGACGGGTACTTGGACCTTCTCAGGGAGAACCAGCTCC TCCCAGGGTTTGAGCTGATGGGCAGCGCCTCGGGCCACTTCACTGACT TTGAGGACAAGCAGCAGGTGTTTGAGTGGAAGGACTTGGTCTCCAGC CTGGCCAGGAGATACATCGGTAGGTACGGACTGGCGCATGTTTCCAA GTGGAACTTCGAGACGTGGAATGAGCCAGACCACCACGACTTTGACA ACGTCTCCATGACCATGCAAGGCTTCCTGAACTACTACGATGCCTGCT GGCGACTCCTTCCACACCCCACCGCGATCCCCGCTGAGCTGGGGCCTC CTGCGCCACTGCCACGACGGTACCAACTTCTTCACTGGGGAGGCGGG CGTGCGGCTGGACTACATCTCCCTCCACAGGAAGGGTGCGCGCAGCT CCATCTCCATCCTGGAGCAGGAGAAGGTCGTCGCGCAGCAGATCCGG CAGCTCTTCCCCAAGTTCGCGGACACCCCCATTTACAACGACGAGGCG GACCCGCTGGTGGGCTGGTCCCTGCCACAGCCGTGGAGGGCGGACGT GACCTACGCGCCATGGTGGTGAAGGTCATCGCGCAGCATCAGAACC TGCTACTGGCCAACACCACCTCCGCCTTCCCCTACGCGCTCCTGAGCA ACGACAATGCCTTCCTGAGCTACCACCCGCACCCCTTCGCGCAGCGCA CAGCTGTTGCGCAAGCCGGTGCTCACGGCCATGGGGCTGCTGGCGCT GCTGGATGAGGAGCAGCTCTGGGCCGAAGTGTCGCAGGCCGGGACCG TCCTGGACAGCAACCACGGTGGGCGTCCTGGCCAGCGCCCACCGC CCCCAGGCCCGCCGACGCCTGGCGCGCGCGCGTGCTGATCTACGC GAGCGACGACCCCGCGCCCCACCCCAACCGCAGCGTCGCGGTGACCC TGCGGCTGCGCGGGTGCCCCCCGGCCCGGCCTGGTCTACGTCACG CGCTACCTGGACAACGGGCTCTGCAGCCCCGACGGCGAGTGGCGGCG CCTGGGCCGGCCGTCTTCCCCACGGCAGAGCAGTTCCGGCGCATGC GCGCGGCTGAGGACCCGGTGGCCGCGCGCCCCCCCTTACCCGCC GGCGGCCGCCTGACCCTGCGCCCCGCGCTGCGGCTGCCGTCGCTTTTG CTGGTGCACGTGTGTGCGCGCCCCGAGAAGCCGCCCGGGCAGGTCAC GCGGCTCCGCCCCTGCCCCTGACCCAAGGGCAGCTGGTTCTGGTCTG GTCGGATGAACACGTGGGCTCCAAGTGCCTGTGGACATACGAGATCC AGTTCTCTCAGGACGGTAAGGCGTACACCCCGGTCAGCAGGAAGCCA TCGACCTTCAACCTCTTTGTGTTCAGCCCAGACACAGGTGCTGTCTCT GGCTCCTACCGAGTTCGAGCCCTGGACTACTGGGCCCGACCAGGCCC CTTCTCGGACCCTGTGCCGTACCTGGAGGTCCCTGTGCCAAGAGGGCC CCCATCCCCGGGCAATCCAT GA

FIG. 80B

Met Arg Pro Leu Arg Pro Arg Ala Ala Leu Leu Ala Leu Leu Ala Ser Leu Leu Ala Ala Pro Pro Val Ala Pro Ala Glu Ala Pro His Leu Val Gln Val Asp Ala Ala Arg Ala Leu Trp Pro Leu Arg Arg Phe Trp Arg Ser Thr Gly Phe Cys Pro Pro Leu Pro His Ser Gln Ala Asp Gln Tyr Val Leu Ser Trp Asp Gln Gln Leu Asn Leu Ala Tyr Val Gly Ala Val Pro His Arg Gly Ile Lys Gln Val Arg Thr His Trp Leu Leu Glu Leu Val Thr Thr Arg Gly Ser Thr Gly Arg Gly Leu Ser Tyr Asn Phe Thr His Leu Asp Gly Tyr Leu Asp Leu Leu Arg Glu Asn Gln Leu Leu Pro Gly Phe Glu Leu Met Gly Ser Ala Ser Gly His Phe Thr Asp Phe Glu Asp Lys Gln Gln Val Phe Glu Trp Lys Asp Leu Val Ser Ser Leu Ala Arg Arg Tyr Ile Gly Arg Tyr Gly Leu Ala His Val Ser Lys Trp Asn Phe Glu Thr Trp Asn Glu Pro Asp His His Asp Phe Asp Asn Val Ser Met Thr Met Gln Gly Phe Leu Asn Tyr Tyr Asp Ala Cys Ser Glu Gly Leu Arg Ala Ala Ser Pro Ala Leu Arg Leu Gly Gly Pro Gly Asp Ser Phe His Thr Pro Pro Arg Ser Pro Leu Ser Trp Gly Leu Leu Arg His Cys His Asp Gly Thr Asn Phe Phe Thr Gly Glu Ala Gly Val Arg Leu Asp Tyr Ile Ser Leu His Arg Lys Gly Ala Arg Ser Ser Ile Ser Ile Leu Glu Gln Glu Lys Val Val Ala Gln Gin Ile Arg Gin Leu Phe Pro Lys Phe Ala Asp Thr Pro Ile Tyr Asn Asp Glu Ala Asp Pro Leu Val Gly Trp Ser Leu Pro Gln Pro Trp Arg Ala Asp Val Thr Tyr Ala Ala Met Val Val Lys Val Ile Ala Gln His Gln Asn Leu Leu Leu Ala Asn Thr Thr Ser Ala Phe Pro Tyr Ala Leu Leu Ser Asn Asp Asn Ala Phe Leu Ser Tyr His Pro His Pro Phe Ala Gln Arg Thr Leu Thr Ala Arg Phe Gln Val Asn Asn Thr Arg Pro Pro His Val Gln Leu Leu Arg Lys Pro Val Leu Thr Ala Met Gly Leu Leu Ala Leu Leu Asp Glu Glu Gln Leu Tro Ala Glu Val Ser Gln Ala Gly Thr Val Leu Asp Ser Asn His Thr Val Gly Val Leu Ala Ser Ala His Arg Pro Gln Gly Pro Ala Asp Ala Trp Arg Ala Ala Val Leu Ile Tyr Ala Ser Asp Asp Thr Arg Ala His Pro Asn Arg Ser Val Ala Val Thr Leu Arg Leu Arg Gly Val Pro Pro Gly Pro Gly Leu Val Tyr Val Thr Arg Tyr Leu Asp Asn Gly Leu Cys Ser Pro Asp Gly Glu Trp Arg Arg Leu Gly Arg Pro Val Phe Pro Thr Ala Glu Gln Phe Arg Arg Met Arg Ala Ala Glu Asp Pro Val Ala Ala Ala Pro Arg Pro Leu Pro Ala Gly Gly Arg Leu Thr Leu Arg Pro Ala Leu Arg Leu Pro Ser Leu Leu Leu Val His Val Cvs Ala Arg Pro Glu Lys Pro Pro Gly Gln Val Thr Arg Leu Arg Ala Leu Pro Leu Thr Gln Gly Gln Leu Val Leu Val Trp Ser Asp Glu His Val Gly Ser Lys Cys Leu Trp Thr Tyr Glu Ile Gln Phe Ser Gln Asp Gly Lys Ala Tyr Thr Pro Val Ser Arg Lys Pro Ser Thr Phe Asn Leu Phe Val Phe Ser Pro Asp Thr Gly Ala Val Ser Gly Ser Tyr Arg Val Arg Ala Leu Asp Tyr Trp Ala Arg Pro Gly Pro Phe Ser Asp Pro Val Pro Tyr Leu Glu Val Pro Val Pro Arg Gly Pro Pro Ser Pro Gly Asn Pro

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FIG. 81A

ATGCAGCTGAGGAACCCAGAACTACATCTGGGCTGCGCGCTTGCGCT TCGCTTCCTGGCCCTCGTTTCCTGGGACATCCCTGGGGCTAGAGCACT AGCGCTTCATGTGCAACCTTGACTGCCAGGAAGAGCCAGATTCCTGC ATCAGTGAGAAGCTCTTCATGGAGATGGCAGAGCTCATGGTCTCAGA AGGCTGGAAGGATGCAGGTTATGAGTACCTCTGCATTGATGACTGTTG GATGGCTCCCCAAAGAGATTCAGAAGGCAGACTTCAGGCAGACCCTC AGCGCTTTCCTCATGGGATTCGCCAGCTAGCTAATTATGTTCACAGCA AAGGACTGA'AGCTAGGGATTTATGCAGATGTTGGAAATAAAACCTGC GCAGGCTTCCCTGGGAGTTTTGGATACTACGACATTGATGCCCAGACC TTTGCTGACTGGGGAGTAGATCTGCTAAAATTTGATGGTTGTTACTGT GACAGTTTGGAAAATTTGGCAGATGGTTATAAGCACATGTCCTTGGCC CTGAATAGGACTGGCAGAAGCATTGTGTACTCCTGTGAGTGGCCTCTT TATATGTGGCCCTTTCAAAAGCCCAATTATACAGAAATCCGACAGTAC TGCAATCACTGGCGAAATTTTGCTGACATTGATGATTCCTGGAAAAGT ATAAAGAGTATCTTGGACTGGACATCTTTTAACCAGGAGAGAATTGTT GATGTTGCTGGACCAGGGGGTTGGAATGACCCAGATATGTTAGTGAT TGGCAACTTTGGCCTCAGCTGGAATCAGCAAGTAACTCAGATGGCCCT CTGGGCTATCATGGCTGCTCCTTTATTCATGTCTAATGACCTCCGACA CATCAGCCCTCAAGCCAAAGCTCTCCTTCAGGATAAGGACGTAATTGC CATCAATCAGGACCCCTTGGGCAAGCAAGGGTACCAGCTTAGACAGG GAGACAACTTTGAAGTGTGGGAACGACCTCTCTCAGGCTTAGCCTGG GCTGTAGCTATGATAAACCGGCAGGAGATTGGTGGACCTCGCTCTTAT ACCATCGCAGTTGCTTCCCTGGGTAAAGGAGTGGCCTGTAATCCTGCC TGCTTCATCACACAGCTCCTCCCTGTGAAAAGGAAGCTAGGGTTCTAT GAATGGACTTCAAGGTTAAGAAGTCACATAAATCCCACAGGCACTGT TTTGCTTCAGCTAGAAAATACAATGCAGATGTCATTAAAAGACTTACT TTAA

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FIG. 81B

Met Gln Leu Arg Asn Pro Glu Leu His Leu Gly Cys Ala Leu Ala Leu Arg Phe Leu Ala Leu Val Ser Trp Asp Ile Pro Gly Ala Arg Ala Leu Asp Asn Gly Leu Ala Arg Thr Pro Thr Met Gly Trp Leu His Trp Glu Arg Phe Met Cys Asn Leu Asp Cys Gln Glu Glu Pro Asp Ser Cys Ile Ser Glu Lys Leu Phe Met Glu Met Ala Glu Leu Met Val Ser Glu Gly Trp Lys Asp Ala Gly Tyr Glu Tyr Leu Cys Ile Asp Asp Cys Trp Met Ala Pro Gln Arg Asp Ser Glu Gly Arg Leu Gln Ala Asp Pro Gln Arg Phe Pro His Gly Ile Arg Gln Leu Ala Asn Tyr Val His Ser Lys Gly Leu Lys Leu Gly Ile Tyr Ala Asp Val Gly Asn Lys Thr Cys Ala Gly Phe Pro Gly Ser Phe Gly Tyr Tyr Asp Ile Asp Ala Gln Thr Phe Ala Asp Trp Gly Val Asp Leu Leu Lys Phe Asp Gly Cys Tyr Cys Asp Ser Leu Glu Asn Leu Âla Asp Gly Tyr Lys His Met Ser Leu Ala Leu Asn Arg Thr Gly Arg Ser Ile Val Tyr Ser Cys Glu Trp Pro Leu Tyr Met Trp Pro Phe Gln Lys Pro Asn Tyr Thr Glu Ile Arg Gln Tyr Cys Asn His Trp Arg Asn Phe Ala Asp Ile Asp Asp Ser Trp Lys Ser Ile Lys Ser Ile Leu Asp Trp Thr Ser Phe Asn Gln Glu Arg Ile Val Asp Val Ala Gly Pro Gly Gly Trp Asn Asp Pro Asp Met Leu Val Ile Gly Asn Phe Gly Leu Ser Trp Asn Gln Gln Val Thr Gln Met Ala Leu Trp Ala Ile Met Ala Ala Pro Leu Phe Met Ser Asn Asp Leu Arg His Ile Ser Pro Gln Ala Lys Ala Leu Leu Gln Asp Lys Asp Val Ile Ala Ile Asn Gln Asp Pro Leu Gly Lys Gln Gly Tyr Gln Leu Arg Gln Gly Asp Asn Phe Glu Val Trp Glu Arg Pro Leu Ser Gly Leu Ala Trp Ala Val Ala Met Ile Asn Arg Gin Glu Ile Gly Gly Pro Arg Ser Tyr Thr Ile Ala Val Ala Ser Leu Gly Lys Gly Val Ala Cys Asn Pro Ala Cys Phe Ile Thr Gln Leu Leu Pro Val Lys Arg Lys Leu Gly Phe Tyr Glu Trp Thr Ser Arg Leu Arg Ser His Ile Asn Pro Thr Gly Thr Val Leu Leu Gln Leu Glu Asn Thr Met Gln Met Ser Leu Lys Asp Leu Leu

FIG. 82A

ATGGCGCCGTCGCCGTCTGGGCCGCCGTCGGACTGGAGCT CTGGGCTGCGGCGCACGCCTTGCCCGCCCAGGTGGCATTTACACCCTA · CGCCCGGAGCCCGGGAGCACATGCCGGCTCAGAGAATACTATGACC AGACAGCTCAGATGTGCTGCAGCAAATGCTCGCCGGGCCAACATGCA AAAGTCTTCTGTACCAAGACCTCGGACACCGTGTGTGACTCCTGTGAG GACAGCACATACACCCAGCTCTGGAACTGGGTTCCCGAGTGCTTGAG CTGTGGCTCCCGCTGTAGCTCTGACCAGGTGGAAACTCAAGCCTGCAC TCGGGAACAGAACCGCATCTGCACCTGCAGGCCCGGCTGGTACTGCG CGCTGAGCAAGCAGGAGGGGTGCCGGCTGTGCGCGCCGCTGCGCAAG TGCCGCCCGGGCTTCGGCGTGGCCAGACCAGGAACTGAAACATCAGA CGTGGTGTGCAAGCCCTGTGCCCCGGGGACGTTCTCCAACACGACTTC ATCCACGGATATTTGCAGGCCCCACCAGATCTGTAACGTGGTGGCCAT CCCTGGGAATGCAAGCATGGATGCAGTCTGCACGTCCACGTCCCCCA CCCGGAGTATGGCCCEAGGGGCAGTACACTTACCCCAGCCAGTGTCC ACACGATCCCAACACACGCAGCCAACTCCAGAACCCAGCACTGCTCC AAGCACCTCCTTCCTGCTCCCAATGGGCCCCAGCCCCCCAGCTGAAGG GAGCACTGGCGACTTCGCTCTTCCAGTTGGACTGATTGTGGGTGTGAC AGCCTTGGGTCTACTAATAATAGGAGTGGTGAACTGTGTCATCATGAC CCAGGTGAAAAAGAAGCCCTTGTGCCTGCAGAGAGAAGCCAAGGTGC CTCACTTGCCTGCCGATAAGGCCCGGGGTACACAGGGCCCCGAGCAG CAGCACCTGCTGATCACAGCGCCGAGCTCCAGCAGCAGCTCCCTGGA GAGCTCGGCCAGTGCGTTGGACAGAAGGGCGCCCACTCGGAACCAGC CACAGGCACCAGGCGTGGAGGCCAGTGGGGCCGGGGAGGCCCGGGC CAGCACCGGGAGCTCAGATTCTTCCCCTGGTGGCCATGGGACCCAGG TCAATGTCACCTGCATCGTGAACGTCTGTAGCAGCTCTGACCACAGCT CACAGTGCTCCTCCCAAGCCAGCTCCACAATGGGAGACACAGATTCC AGCCCCTCGGAGTCCCCGAAGGACGAGCAGGTCCCCTTCTCCAAGGA GGAATGTGCCTTTCGGTCACAGCTGGAGACGCCAGAGACCCTGCTGG GGAGCACCGAAGAGAAGCCCCTGCCCCTTGGAGTGCCTGATGCTGGG ATGAAGCCCAGTTAACCAGGCCGGTGTGGGCTGTGTCGTAGCCAAGG TGGGCTGAGCCCTGGCAGGATGACCCTGCGAAGGGGCCCTGGTCCTT CCAGGC

FIG. 82B

Met Ala Pro Val Ala Val Trp Ala Ala Leu Ala Val Gly Leu Glu Leu Trp Ala Ala Ala His Ala Leu Pro Ala Gln Val Ala Phe Thr Pro Tyr Ala Pro Glu Pro Gly Ser Thr Cys Arg Leu Arg Glu Tyr Tyr Asp Gln Thr Ala Gln Met Cys Cys Ser Lys Cys Ser Pro Gly Gln His Ala Lys Val Phe Cys Thr Lys Thr Ser Asp Thr Val Cys Asp Ser Cys Glu Asp Ser Thr Tyr Thr Gln Leu Trp Asn Trp Val Pro Glu Cys Leu Ser Cys Gly Ser Arg Cys Ser Ser Asp Gln Val Glu Thr Gln Ala Cys Thr Arg Glu Gln Asn Arg Ile Cys Thr Cys Arg Pro Gly Trp Tyr Cys Ala Leu Ser Lys Gln Glu Gly Cys Arg Leu Cys Ala Pro Leu Arg Lys Cys Arg Pro Gly Phe Gly Val Ala Arg Pro Gly Thr Glu Thr Ser Asp Val Val Cys Lys Pro Cys Ala Pro Gly Thr Phe Ser Asn Thr Thr Ser Ser Thr Asp Ile Cys Arg Pro His Gln Ile Cys Asn Val Val Ala Ile Pro Gly Asn Ala Ser Met Asp Ala Val Cys Thr Ser Thr Ser Pro Thr Arg Ser Met Ala Pro Gly Ala Val His Leu Pro Gln Pro Val Ser Thr Arg Ser Gln His Thr Gln Pro Thr Pro Glu Pro Ser Thr Ala Pro Ser Thr Ser Phe Leu Leu Pro Met Gly Pro Ser Pro Pro Ala Glu Gly Ser Thr Gly Asp Phe Ala Leu Pro Val Gly Leu Ile Val Gly Val Thr Ala Leu Gly Leu Leu Ile Ile Gly Val Val Asn Cys Val lle Met Thr Gln Val Lys Lys Pro Leu Cys Leu Gln Arg Glu Ala Lys Val Pro His Leu Pro Ala Asp Lys Ala Arg Gly Thr Gln Gly Pro Glu Gln Gln His Leu Leu Ile Thr Ala Pro Ser Ser Ser Ser Ser Leu Glu Ser Ser Ala Ser Ala Leu Asp Arg Arg Ala Pro Thr Arg Asn Gln Pro Gln Ala Pro Gly Val Glu Ala Ser Gly Ala Gly Glu Ala Arg Ala Ser Thr Gly Ser Ser Asp Ser Ser Pro Gly Gly His Gly Thr Gln Val Asn Val Thr Cys Ile Val Asn Val Cys Ser Ser Ser Asp His Ser Ser Gln Cys Ser Ser Gln Ala Ser Ser Thr Met Gly Asp Thr Asp Ser Ser Pro Ser Glu Ser Pro Lys Asp Glu Gln Val Pro Phe Ser Lys Glu Glu Cys Ala Phe Arg Ser Gln Leu Glu Thr Pro Glu Thr Leu Leu Gly Ser Thr Glu Glu Lys Pro Leu Pro Leu Gly Val Pro Asp Ala Gly Met Lys Pro Ser

FIG. 83A

Asp Ile Gin Met Thr Gin Ser Pro Ser Ser Leu Ser Ala Ser Val Giy Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gin Asp Val Asn Thr Ala Val Ala Trp Tyr Gin Gin Lys Pro Giy Lys Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Phe Leu Tyr Ser Giy Val Pro Ser Arg Phe Ser Giy Ser Arg Ser Giy Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gin Pro Giu Asp Phe Ala Thr Tyr Tyr Cys Gin Gin His Tyr Thr Thr Pro Pro Thr Phe Giy Gil Gily Thr Lys Val Giu Ile Lys

FIG. 83B

Giu Val Gin Leu Val Giu Ser Giy Gly Gly Leu Val Gin Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr Tyr Ile His Trp Val Arg Gin Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser WO 2004/099231 PCT/US2004/011494

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FIG. 84A.

Gih Val Tir Leu Arg Giu Ser Gly Pro Ala Leu Val Lys Pro Thr Gin Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser Gly Met Ser Val Gly Tri le Arg Gin Pro Ser Gly Lys Ala Leu Glu Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asp Gin Val Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Try Tyr Cys Ala Arg Ser Met Ile Thr Asn Trp Tyr Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser

FIG. 84B

Asp Ile Gin Met Thr Gin Ser Pro Ser Thr Leu Ser Ala Ser Val Giy Asp Arg Val Thr Ile Thr Cys Lys Cys Gin Leu Ser Val Giy Tyr Met His Trp Tyr Gin Gin Lys Pro Giy Lys Ala Pro Lys Leu Trp Ile Tyr Asp Thr Ser Lys Leu Ala Ser Giy Val Pro Ser Arg Phe Ser Giy Ser Giy Ser Giy Thr Giv Phe Thr Leu Thr Ile Ser Ser Leu Gin Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Phe Gin Giy Ser Giy Tyr Pro Phe Thr Phe Giy Giy Giy Thr Lys Leu Giu Ile Lys

FIG. 85A

GACATCITGCTGACTCAGTCTCCAGCCATCCTGTCTGTGAGTCCAGGA
GAAAGAGTCAGTTTCTCCTGCAGGGCCAGTCAGTTCGTTGAGTCCAGGA
GAAAGAGTCAGTTTCTCCTGCAGGGCCAGTCAGTTCGTTGGCTCAAGC
ATCCACTGGTATCAGCAAAAAAGGTCTCTCCAAGGCTTCTCATA
AAGTATGCTTCTGAGTCTATGTCTGGGATCCCTTCCAGGTTTAGTGGC
AGTGGATCAGGACAAATTTACTCTTCACACAACACTGTGGAGTCT
GAAGATATTGCAGATTATTACTGTCAACAAAGTCATAGCTGGCCATTC
ACGTTCGGCTCGGGGACAAATTTGGAAGTAAAAGAAGTGAAACTTGA
GGAGTCTGGAGGAGGACAAATTTGGAAGTCATGAAACTCT
CCTGTGTTGCCTCTGGATTCATTTTCAGTAACCACTGGATGAACTGGG
TCCGCCAGTCTCCAGAGAAGGGGCTTGATGGTTTCTGAAATTAGA
TCAAAAATCTATTAATTCTGCAACACATTATGCGGAGTCTGTGAAAGGG
AGGTTCACCATCTCAAGAGATGATTCCAAAAGTGCTGTCTACCTGCAA
ATGACCGACTTAAGAACTGAAGACACTGGGGTTTATTACTGTTCCAGG
AATTACTACTAGTAGAACTGAAGACACTGGGGCCAAGGCACCACTCTC
ACAGTCTCC

FIG. 85B

Asp lle Leu Leu Thr Gin Ser Pro Ala Ile Leu Ser Val Ser Pro Gly Giu Arg Val Ser Phe Ser Cys Arg Ala Ser Gin Phe Val Gly Ser Ser Ile His Trp Tyr Gin Gin Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile Lys Tyr Ala Ser Giu Ser Met Ser Giy Ile Pro Ser Arg Phe Ser Giy Ser Giy Ser Giy Thr, Asp Phe Thr Leu Ser Ile Asn Thr Val Giu Ser Giu Asp Ile Ala Asp Tyr Tyr Cys Gin Gin Ser His Ser Trp Pro Phe Thr Phe Gly Ser Giy Thr Asn Leu Giu Val Lys Giu Val Lys Leu Giu Giu Ser Gly Gly Giy Leu Val Gin Pro Gly Gly Ser Met Lys Leu Ser Cys Val Ala Ser Gly Phe Ile Phe Ser Asn His Trp Met Asn Trp Val Arg Gin Ser Fro Giu Lys Giy Leu Giu Trp Val Ala Giu Ile Arg Ser Lys Ser Ile Asn Ser Ala Thr His Tyr Ala Giu Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ala Val Tyr LeuGin Met Thr Asp Leu Arg Thr Giu Asp Thr Giy Val Tyr Tyr Cys Ser Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Giy Gin Giy Thr Thr Leu Thr Val Ser

FIG. 86A

ATGGAGACAGACACTCCTGTTATGGGTGCTGCTGCTCTGGGTTCCA GGTTCCACTGGTGACGTCAGGCGAGGCCCCGGAGCCTGCGGGGCAG GGACGCCCACGCCCTGCGTCCCGGCCGAGTGCTTCGACC TGCTGGTCCGCCACTGCGTGGCCTGCGGGCTCCTGCGCACGCCGCGGC CGAAACCGGCCGGGCCAGCAGCCCTGCGCCCAGGACGCCCTGCAG CCGCAGGAGTCGGTGGGCGCGGGGGGCGGCGGCGGCGGCGACA AAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGA CCGTCAGTCTTCCTCTTCCCCCAAAACCCAAGGACACCCTCATGATC TCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGA AGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGC ATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTA CCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGG CAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCA TCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAG GTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGT CAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGT GGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACG CCTCCCGTGTTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTC ACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTC CGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCT CCCTGTCTCCCGGGAAATGA

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FIG. 86B

Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro Gly Ser Thr Gly Asp Val Arg Arg Gly Pro Arg Ser Leu Arg Gly Arg Asp Ala Pro Ala Pro Thr Pro Cys Val Pro Ala Glu Cys Phe Asp Leu Leu Val Arg His Cys Val Ala Cys Gly Leu Leu Arg Thr Pro Arg Pro Lys Pro Ala Gly Ala Ser Ser Pro Ala Pro Arg Thr Ala Leu Gln Pro Gln Glu Ser Val Gly Ala Gly Ala Gly Glu Ala Ala Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

FIG. 87

Asp Ile Gin Met Thr Gin Thr Thr Ser Ser Leu Ser Ala Ser Leu Giy Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gin Asp Ile Asn Asn Tyr Leu Asn Trp Tyr Gin Gin Lys Pro Asp Giy Ile Val Lys Leu Leu Ile Tyr Tyr Thr Ser Thr Leu His Ser Giy Val Pro Ser Arg Phe Ser Giy Ser Giy Ser Giy Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Giu Gin Giu Asp Ile Ala Thr Tyr Phe Cys Gin Gin Giy Asn Thr Leu Pro Trp Thr Phe Giy Giy Giv Thr Lys Leu Giu Ile Lys

FIG. 88

Gin Val Gin Leu Gin Gin Ser Gly Ala Glu Leu Val Gly Pro Gly Thr Ser Val Arg Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn Tyr Leu Ile Glu Trp Val Lys Gin Arg Pro Gly Gin Gly Leu Glu Trp Ile Gly Val Ile Tyr Pro Gly Ser Gly Gly Thr Asn Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Asp Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Asp Gly Asn Tyr Gly Trp Phe Ala Tyr Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ala

FIG. 89

Asp Ile Gin Met Thr Gin Thr Pro Ser Thr Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gin Asp Ile Asn Asn Tyr Leu Asn Trp Tyr Gin Gin Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Tyr Thr Ser Thr Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gin Pro Asp Asp Phe Ala Thr Tyr Phe Cys Gin Gin Gly Asn Thr Leu Pro Trp Thr Phe Gly Gin Gly Thr Lys Val Glu Val Lys

FIG. 90

Gìn Val Gìn Leu Val Gìn Ser Gly Ala Glu Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn Tyr Leu lle Glu Trp Val·Arg Gìn Ala Pro Gly Gìn Gly Leu Glu Trp Ile Gly Val Ile Tyr Pro Gly Ser Gly Gly Thr Asn Tyr Asn Glu Lys Phe Lys Gly Arg Val Thr Leu Thr Val Asp Glu Ser Thr Asn Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Phe Cys Ala Arg Arg Asp Gly Asn Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser

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Asp Ile Gln Met Thr Gln Thr Pro Ser Thr Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Asn Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Tyr Thr Ser Thr Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Val Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys

FIG. 92

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn Tyr Leu Ile Glu Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Val Ile Tvr Pro Gly Ser Gly Gly Thr Asn Tyr Asn Glu Lys Phe Lys Gly Arg Val Thr Leu Thr Val Asp Glu Ser Thr Asn Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Phe Cys Ala Arg Arg Asp Gly Asn Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gin Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Glu Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly

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FIG. 93A

FIG. 93B

Met Asp Phe Gin Val Gin IIe IIe Ser Phe Leu Leu IIe Ser Ala Ser Val IIe Met Ser Arg Gily Gin IIe Val Leu Ser Gin Ser Pro Ala IIe Leu Ser Ala Ser Pro Gily Giu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Ser Val Ser Tyr IIe His Trp Phe Gin Gin Lys Pro Gily Ser Ser Pro Lys Pro Trp IIe Tyr Ala Thr Ser Asn Leu Ala Ser Gily Val Pro Val Arg Phe Ser Gily Ser Gily Ser Gily Thr Ser Tyr Ser Leu Thr IIe Ser Arg Val Giu Ala Giu Asp Ala Ala Thr Tyr Tyr Cys Gin Gin Trp Thr Ser Asn Pro Pro Thr Phe Gily Gily Gily Thr Lys Leu Giu IIe Lys

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FIG. 94A

FIG. 94B

Met Gly Trp Ser Leu Ile Leu Leu Phe Leu Val Ala Val Ala Thr Arg Val Leu Ser Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Asn Met His Trp Val Lys Gln Thr Pro Gly Arg Gly Leu Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ala

FIG. 95A

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GACGTCGCGGCCGCTCTAGGCCTCCAAAAAAGCCTCCTCACTACTTCT AAAATTAGTCAGCCATGCATGGGGCGGAGAATGGGCGGAACTGGGCG GAGTTAGGGGCGGATGGGCGGAGTTAGGGGCGGGACTATGGTTGCT GACTAATTGAGATGCATGCTTTGCATACTTCTGCCTGCTGGGGAGCCT ATACTTCTGCCTGCTGGGGAGCCTGGGGACTTTCCACACCCTAACTGA CACACATTCCACAGAATTAATTCCCCTAGTTATTAATAGTAATCAATT ACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAA CTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCCC ATTGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGA CTTTCCATTGACGTCAATGGGTGGACTATTTACGGTAAACTGCCCACT TGGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACG TCAATGACGGTAAATGGCCCGCCTGGCATTATGCCCAGTACATGACCT TATGGGACTTTCCTACTTGGCAGTACATCTACGTATTAGTCATCGCTA TTACCATGGTGATGCGGTTTTGGCAGTACATCAATGGGCGTGGATAGC GGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGACGTCAATG GGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCGTA ACAACTCCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGTGG GAGGTCTATATAAGCAGAGCTGGGTACGTGAACCGTCAGATCGCCTG GAGACGCCATCACAGATCTCTCACCATGAGGGTCCCCGCTCAGCTCCT GGGGCTCCTGCTCTGGCTCCCAGGTGCACGATGTGATGGTACCAA GGTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCC GCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCT GCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGG ATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAG GACAGCAAGGACACCTACAGCCTCAGCAGCACCCTGACGCTGAG CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCC ATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAG TGTTGAATTCAGATCCGTTAACGGTTACCAACTACCTAGACTGGATTC GTGACAACATGCGGCCGTGATATCTACGTATGATCAGCCTCGACTGTG CCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCCCTCCCCCGTGCCTTCCT TGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAATAAAATGAGG AAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGTG GGGTGGGGCAGGACAGCAAGGGGGGGGGATTGGGAAGACAATAGCAG GCATGCTGGGGATGCGGTGGGCTCTATGGAACCAGCTGGGGCTCGAC AGCTATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGC CCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTT GGCAGTACATCTACGTATTAGTCATCGCTATTACCATGGTGATGCGGT TTTGGCAGTACATCAATGGGCGTGGATAGCGGTTTGACTCACGGGGA

FIG. 95B

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CAAAATCAACGGGACTTTCCAAAATGTCGTAACAACTCCGCCCCATTG ACGCAAATGGGCGTAGGCGTGTACGGTGGGAGGTCTATATAAGCAG AGCTGGGTACGTCCTCACATTCAGTGATCAGCACTGAACACAGACCC GTCGACATGGGTTGGAGCCTCATCTTGCTCTTCCTTGTCGCTGTTGCTA CGCGTGTCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCT CCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTC AAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGC CCTGACCAGCGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGG ACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGG CACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCA AGGTGGACAAGAAGCAGAGCCCAAATCTTGTGACAAAACTCACACA TGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTC CTCTTCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCT GAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGT CAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGA CAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGC GTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGACTACAA GTGCAAGGTCTCCAACAAGCCCTCCCAGCCCCCATCGAGAAAACCA TCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTG CCCCATCCCGGGATGAGCTGACCAGGAACCAGGTCAGCCTGACCTG CCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGA GCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTG GACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAG AGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGA GGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGG TAAATGAGGATCCGTTAACGGTTACCAACTACCTAGACTGGATTCGTG ACAACATGCGGCCGTGATATCTACGTATGATCAGCCTCGACTGTGCCT CCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAATAAAATGAGGAAA TTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGTGGGG TGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCA TGCTGGGGATGCGGTGGGCTCTATGGAACCAGCTGGGGCTCGACAGC GCTGGATCTCCCGATCCCCAGCTTTGCTTCTCAATTTCTTATTTGCATA ATGAGAAAAAAAGGAAAATTAATTTTAACACCAATTCAGTAGTTGAT TGAGCAAATGCGTTGCCAAAAAGGATGCTTTAGAGACAGTGTTCTCT GCACAGATAAGGACAAACATTATTCAGAGGGAGTACCCAGAGCTGAG ACTCCTAAGCCAGTGAGTGGCACAGCATTCTAGGGAGAAATATGCTT GTCATCACCGAAGCCTGATTCCGTAGAGCCACACCTTGGTAAGGGCC AATCTGCTCACACAGGATAGAGAGGGCAGGAGCCAGGGCAGAGCAT ATAAGGTGAGGTAGGATCAGTTGCTCCTCACATTTGCTTCTGACATAG TTGTGTTGGGAGCTTGGATAGCTTGGACAGCTCAGG

FIG. 95C

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GCTGCGATTTCGCGCCAAACTTGACGGCAATCCTAGCGTGAAGGCTG GTAGGATTTTATCCCCGCTGCCATCATGGTTCGACCATTGAACTGCAT CGTCGCCGTGTCCCAAAATATGGGGATTGGCAAGAACGGAGACCTAC CCTGGCCTCCGCTCAGGAACGAGTTCAAGTACTTCCAAAGAATGACC ACAACCTCTTCAGTGGAAGGTAAACAGAATCTGGTGATTATGGGTAG GAAAACCTGGTTCTCCATTCCTGAGAACAATCGACCTTTAAAGGACA GAATTAATATAGTTCTCAGTAGAGAACTCAAAGAACCACCACGAGGA GCTCATTTTCTTGCCAAAAGTTTGGATGATGCCTTAAGACTTATTGAA CAACCGGAATTGGCAAGTAAAGTAGACATGGTTTGGATAGTCGGAGG CAGTTCTGTTTACCAGGAAGCCATGAATCAACCAGGCCACCTTAGACT CTTTGTGACAAGGATCATGCAGGAATTTGAAAGTGACACGTTTTTCCC AGAAATTGATTTGGGGAAATATAAACTTCTCCCAGAATACCCAGGCG TCCTCTCTGAGGTCCAGGAGGAAAAAGGCATCAAGTATAAGTTTGAA GTCTACGAGAAGAAGACTAACAGGAAGATGCTTTCAAGTTCTCTGC TCCCCTCCTAAAGTCATGCATTTTTATAAGACCATGGGACTTTTGCTG TTGCCCCTCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCAC TGTCCTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAG AGGATTGGGAAGACAATAGCAGGCATGCTGGGGATGCGGTGGGCTCT ATGGAACCAGCTGGGGCTCGAGCTACTAGCTTTGCTTCTCAATTTCTT ATTTGCATAATGAGAAAAAAAGGAAAATTAATTTTAACACCAATTCA GTAGTTGATTGAGCAAATGCGTTGCCAAAAAGGATGCTTTAGAGACA GTGTTCTCTGCACAGATAAGGACAAACATTATTCAGAGGGAGTACCC AGAGCTGAGACTCCTAAGCCAGTGAGTGGCACAGCATTCTAGGGAGA AATATGCTTGTCATCACCGAAGCCTGATTCCGTAGAGCCACACCTTGG TAAGGGCCAATCTGCTCACACAGGATAGAGAGGGCAGGAGCCAGGG CAGAGCATATAAGGTGAGGTAGGATCAGTTGCTCCTCACATTTGCTTC TGACATAGTTGTGTTGGGAGCTTGGATCGATCCTCTATGGTTGAACAA GATGGATTGCACGCAGGTTCTCCGGCCGCTTGGGTGGAGAGGCTATTC GGCTATGACTGGGCACAACAGACAATCGGCTGCTCTGATGCCGCCGT GTTCCGGCTGTCAGCGCAGGGGCGCCCGGTTCTTTTTGTCAAGACCGA CCTGTCCGGTGCCCTGAATGAACTGCAGGACGAGGCAGCGCGGCTAT CGTGGCTGGCCACGACGGCGTTCCTTGCGCAGCTGTGCTCGACGTTG TCACTGAAGCGGAAGGGACTGCTGCTATTGGGCGAAGTGCCGGGG CAGGATCTCCTGTCATCTCACCTTGCTCCTGCCGAGAAAGTATCCATC ATGGCTGATGCAATGCGGCGGCTGCATACGCTTGATCCGGCTACCTGC CCATTCGACCACCAAGCGAAACATCGCATCGAGCGAGCACGTACTCG GATGGAAGCCGGTCTTGTCGATCAGGATGATCTGGACGAAGAGCATC AGGGGCTCGCGCCAGCCGAACTGTTCGCCAGGCTCAAGGCGCGCATG CCCGACGGCGAGGATCTCGTCGTGACCCATGGCGATGCCTGCTTGCCG

FIG. 95D

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AATATCATGGTGGAAAATGGCCGCTTTTCTGGATTCATCGACTGTGGC CGGCTGGGTGTGGCGGACCGCTATCAGGACATAGCGTTGGCTACCCG TGATATTGCTGAAGAGCTTGGCGGCGAATGGGCTGACCGCTTCCTCGT GCTTTACGGTATCGCCGCTTCCCGATTCGCAGCGCATCGCCTTCTATC GCCTTCTTGACGAGTTCTTCTGAGCGGGACTCTGGGGTTCGAAATGAC CGACCAAGCGACGCCAACCTGCCATCACGAGATTTCGATTCCACCG CCGCCTTCTATGAAAGGTTGGGCTTCGGAATCGTTTTCCGGGACGCCG GCTGGATGATCCTCCAGCGCGGGGATCTCATGCTGGAGTTCTTCGCCC ACCCCAACTTGTTTATTGCAGCTTATAATGGTTACAAATAAAGCAATA GCATCACAAATTTCACAAATAAAGCATTTTTTTCACTGCATTCTAGTT GTGGTTTGTCCAAACTCATCAATCTATCTTATCATGTCTGGATCGCGG CCGCGATCCCGTCGAGAGCTTGGCGTAATCATGGTCATAGCTGTTTCC TGTGTGAAATTGTTATCCGCTCACAATTCCACACACACATACGAGCCGG AGCATAAAGTGTAAAGCCTGGGGTGCCTAATGAGTGAGCTAACTCAC ATTAATTGCGTTGCGCTCACTGCCCGCTTTCCAGTCGGGAAACCTGTC GTGCCAGCTGCATTAATGAATCGGCCAACGCGCGGGGAGAGGCGGTT TGCGTATTGGGCGCTCTTCCGCTTCCTCGCTCACTGACTCGCTGCGCTC GGTCGTTCGGCTGCGGCGAGCGGTATCAGCTCACTCAAAGGCGGTAA TACGGTTATCCACAGAATCAGGGGATAACGCAGGAAAGAACATGTGA GCAAAAGGCCAGCAAAAGGCCAGGAACCGTAAAAAGGCCGCGTTGC TGGCGTTTTTCCATAGGCTCCGCCCCCCTGACGAGCATCACAAAAATC GACGCTCAAGTCAGAGGTGGCGAAACCCGACAGGACTATAAAGATAC CAGGCGTTTCCCCCTGGAAGCTCCCTCGTGCGCTCTCCTGTTCCGACC CTGCCGCTTACCGGATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTG GCGCTTTCTCAATGCTCACGCTGTAGGTATCTCAGTTCGGTGTAGGTC GTTCGCTCCAAGCTGGGCTGTGTGCACGAACCCCCCGTTCAGCCCGAC CGCTGCGCCTTATCCGGTAACTATCGTCTTGAGTCCAACCCGGTAAGA CACGACTTATCGCCACTGGCAGCAGCCACTGGTAACAGGATTAGCAG AGCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGCCTA ACTACGGCTACACTAGAAGGACAGTATTTGGTATCTGCGCTCTGCTGA AGCCAGTTACCTTCGGAAAAAGAGTTGGTAGCTCTTGATCCGGCAAA CAAACCACCGCTGGTAGCGGTGGTTTTTTTGTTTGCAAGCAGCAGATT ACGCGCAGAAAAAAAGGATCTCAAGAAGATCCTTTGATCTTTCTAC GGGGTCTGACGCTCAGTGGAACGAAAACTCACGTTAAGGGATTTTGG TCATGAGATTATCAAAAAGGATCTTCACCTAGATCCTTTTAAATTAAA AATGAAGTTTTAAATCAATCTAAAGTATATATGAGTAAACTTGGTCTG ACAGTTACCAATGCTTAATCAGTGAGGCACCTATCTCAGCGATCTGTC TATTTCGTTCATCCATAGTTGCCTGACTCCCCGTCGTGTAGATAACTAC GATACGGGAGGGCTTACCATCTGGCCCCAGTGCTGCAATGATACCGC GAGACCCACGCTCACCGGCTCCAGATTTATCAGCAATAAACCAGCCA GCCGGAAGGCCGAGCGCAGAAGTGGTCCTGCAACTTTATCCGCCTC

FIG. 95E

GACGTCGCGCCCTCTAGGCCTCCAAAAAAGCCTCCTCACTACTTCT AAAATTAGTCAGCCATGCATGGGGGGGGAGAATGGGCGGAACTGGGCG GAGTTAGGGGGGGATTGGCTGGTTAGGGGGGGGACTATGGTTGCT GACTAATTGAGATGCATGCTTTGCATACTTCTGCCTGCTGGGGAGCCT ATACTTCTGCCTGCTGGGGAGCCTGGGGACTTTCCACACCCTAACTGA CACACATTCCACAGAATTAATTCCCCTAGTTATTAATAGTAATCAATT ACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAA ATTGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGA CTTTCCATTGACGTCAATGGGTGGACTATTTACGGTAAACTGCCCACT TGGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACG TCAATGACGGTAAATGGCCCGCCTGGCATTATGCCCAGTACATGACCT TATGGGACTTTCCTACTTGGCAGTACATCTACGTATTAGTCATCGCTA TTACCATGGTGATGCGGTTTTGGCAGTACATCAATGGGCGTGGATACC GGTTTGACTCACGCGGATTTCCAAGTCTCCACCCCATTGACGTCAATG GGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCGTA ACAACTCCGCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGTGG GAGGTCTATATAAGCAGAGCTGGGTACGTGAACCGTCAGATCGCCTG GAGACGCCATCACAGATCTCTCACTATGGATTTTCAGGTGCAGATTAT CAGCTTCCTGCTAATCAGTGCTTCAGTCATAATGTCCAGAGGACAAAT TGTTCTCCCAGTCTCCAGCAATCCTGTCTGCATCTCCAGGGGAGAA GGTCACAATGACTTGCAGGGCCAGCTCAAGTGTAAGTTACATCCACT GGTTCCAGCAGAAGCCAGGATCCTCCCCCAAACCCTGGATTTATGCCA CATCCAACCTGGCTTCTGGAGTCCCTGTTCGCTTCAGTGGCAGTGGGT CTGGGACTTCTTACTCTCTCACAATCAGCAGAGTGGAGGCTGAAGATG GAGGGGGACCAAGCTGGAAATCAAACGTACGGTGGCTGCACCATCT GTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCC TCTGTTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTA CAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAG TGTCACAGAGCAGGACAGCAAGGACACCTACAGCCTCAGCAGCA CCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCC TGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTT CAACAGGGGAGAGTGTTGAATTCAGATCCGTTAACGGTTACCAACTA CCTAGACTGGATTCGTGACAACATGCGGCCGTGATATCTACGTATGAT CAGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCCTC CCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCC

FIG. 96B

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TAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCT ATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGG AAGACAATAGCAGGCATGCTGGGGATGCGGTGGGCTCTATGGAACCA GCTGGGGCTCGACAGCTATGCCAAGTACGCCCCCTATTGACGTCAATG ACGGTAAATGGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGG ACTTTCCTACTTGGCAGTACATCTACGTATTAGTCATCGCTATTACCAT GGTGATGCGGTTTTGGCAGTACATCAATGGGCGTGGATAGCGGTTTG ACTCACGGGGATTTCCAAGTCTCCACCCCATTGACGTCAATGGGAGTT TGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCGTAACAACT CCGCCCATTGACGCAAATGGGCGTAGGCGTGTACGGTGGGAGGTC TATATAAGCAGAGCTGGGTACGTCCTCACATTCAGTGATCAGCACTGA ACACAGACCCGTCGACATGGGTTGGAGCCTCATCTTGCTCTTGT CGCTGTTGCTACGCGTGTCCTGTCCCAGGTACAACTGCAGCAGCCTGG GGCTGAGCTGGAAGCCTGGGGCCTCAGTGAAGATGTCCTGCAAGG CTTCTGGCTACACATTTACCAGTTACAATATGCACTGGGTAAAACAGA CACCTGGTCGGGGCCTGGAATGGATTGGAGCTATTTATCCCGGAAAT GGTGATACTTCCTACAATCAGAAGTTCAAAGGCAAGGCCACATTGAC TGCAGACAAATCCTCCAGCACAGCCTACATGCAGCTCAGCAGCCTGA CATCTGAGGACTCTGCGGTCTATTACTGTGCAAGATCGACTTACTACG GCGGTGACTGCTACTTCAATGTCTGGGGCGCAGGGACCACGGTCACC GTCTCTGCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCC TCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGT CAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCG CCCTGACCAGCGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAG GACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGG GCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACC AAGGTGGACAAGAAAGCAGAGCCCAAATCTTGTGACAAAACTCACAC ATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTT CCTCTTCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCC TGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGG TCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAG ACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAG CGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACA AGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACC ATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCT GCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCT GCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAG AGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCT GGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAA GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATG AGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGG GTAAATGAGGATCCGTTAACGGTTACCAACTACCTAGACTGGATTCGT

FIG. 96C

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GACAACATGCGGCCGTGATATCTACGTATGATCAGCCTCGACTGTGCC ACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAATAAAATGAGGAA ATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGGTGGG GTGGGGCAGGACAGCAAGGGGGGGGGATTGGGAAGACAATAGCAGGC ATGCTGGGGATGCGGTGGGCTCTATGGAACCAGCTGGGGCTCGACAG CGCTGGATCTCCCGATCCCCAGCTTTGCTTCTCAATTTCTTATTTGCAT AATGAGAAAAAAGGAAAATTAATTTTAACACCAATTCAGTAGTTGA TTGAGCAAATGCGTTGCCAAAAAGGATGCTTTAGAGACAGTGTTCTCT GCACAGATAAGGACAAACATTATTCAGAGGGAGTACCCAGAGCTGAG ACTCCTAAGCCAGTGAGTGGCACAGCATTCTAGGGAGAAATATGCTT GTCATCACCGAAGCCTGATTCCGTAGAGCCACACCTTGGTAAGGGCC AATCTGCTCACACAGGATAGAGAGGGCAGGAGCCAGGGCAGAGCAT ATAAGGTGAGGTAGGATCAGTTGCTCCTCACATTTGCTTCTGACATAG TTGTGTTGGGAGCTTGGATAGCTTGGACAGCTCAGGGCTGCGATTTCG CGCCAAACTTGACGGCAATCCTAGCGTGAAGGCTGGTAGGATTTTATC CCCGCTGCCATCATGGTTCGACCATTGAACTGCATCGTCGCCGTGTCC CAAAATATGGGGATTGGCAAGAACGGAGACCTACCCTGGCCTCCGCT CAGGAACGAGTTCAAGTACTTCCAAAGAATGACCACAACCTCTTCAG TGGAAGGTAAACAGAATCTGGTGATTATGGGTAGGAAAACCTGGTTC TCCATTCCTGAGAAGAATCGACCTTTAAAGGACAGAATTAATATAGTT CTCAGTAGAGAACTCAAAGAACCACCACGAGGAGCTCATTTTCTTGC CAAAAGTTTGGATGATGCCTTAAGACTTATTGAACAACCGGAATTGG CAAGTAAAGTAGACATGGTTTGGATAGTCGGAGGCAGTTCTGTTTACC AGGAAGCCATGAATCAACCAGGCCACCTTAGACTCTTTGTGACAAGG ATCATGCAGGAATTTGAAAGTGACACGTTTTTCCCAGAAATTGATTTG GGGAAATATAAACTTCTCCCAGAATACCCAGGCGTCCTCTCTGA GGTCCAGGAGAAAAAGGCATCAAGTATAAGTTTGAAGTCTACGAGA AGAAAGACTAACAGGAAGATGCTTTCAAGTTCTCTGCTCCCCTCCTAA AGCTATGCATTTTTATAAGACCATGGGACTTTTGCTGGCTTTAGATCA GCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCCCTCCC CCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTA ATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTAT TCTGGGGGTGGGGTGGGCAGGACAGCAAGGGGGAGGATTGGGAA GACAATAGCAGGCATGCTGGGGATGCGGTGGGCTCTATGGAACCAGC TGGGGCTCGAGCTACTAGCTTTGCTTCTCAATTTCTTATTTGCATAATG GCAAATGCGTTGCCAAAAAGGATGCTTTAGAGACAGTGTTCTCTGCA CAGATA AGGACA AACATTATTCAGAGGGAGTACCCAGAGCTGAGACT CCTAAGCCAGTGAGTGGCACAGCATTCTAGGGAGAAATATGCTTGTC ATCACCGAAGCCTGATTCCGTAGAGCCACACCTTGGTAAGGGCCAAT CTGCTCACACAGGATAGAGAGGGCAGGAGCCAGGGCAGAGCATATA AGGTGAGGTAGGATCAGTTGCTCCTCACATTTGCTTCTGACATAGTTG

FIG. 96D

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TGTTGGGAGCTTGGATCGATCCTCTATGGTTGAACAAGATGGATTGCA CGCAGGTTCTCCGGCCGCTTGGGTGGAGAGGCTATTCGGCTATGACTG GGCACAACAGACAATCGGCTGCTCTGATGCCGCCGTGTTCCGGCTGTC AGCGCAGGGGCCCCGGTTCTTTTTGTCAAGACCGACCTGTCCGGTGC CGACGGGCGTTCCTTGCGCAGCTGTGCTCGACGTTGTCACTGAAGCGG GAAGGGACTGCTATTGGGCGAAGTGCCGGGGCAGGATCTCCTG TCATCTCACCTTGCTCCTGCCGAGAAAGTATCCATCATGGCTGATGCA ATGCGGCGCTGCATACGCTTGATCCGGCTACCTGCCCATTCGACCAC CAAGCGAAACATCGCATCGAGCGAGCACGTACTCGGATGGAAGCCGG TCTTGTCGATCAGGATGATCTGGACGAAGAGCATCAGGGGCTCGCGC CAGCCGAACTGTTCGCCAGGCTCAAGGCGCGCATGCCCGACGGCGAG GATCTCGTCGTGACCCATGGCGATGCCTGCTTGCCGAATATCATGGTG GAAAATGGCCGCTTTTCTGGATTCATCGACTGTGGCCGGCTGGGTGTG GCGGACCGCTATCAGGACATAGCGTTGGCTACCCGTGATATTGCTGA AGAGCTTGGCGGCGAATGGGCTGACCGCTTCCTCGTGCTTTACGGTAT CGCCGCTCCCGATTCGCAGCGCATCGCCTTCTATCGCCTTCTTGACGA GCCCAACCTGCCATCACGAGATTTCGATTCCACCGCCGCCTTCTATGA AAGGTTGGGCTTCGGAATCGTTTTCCGGGACGCCGGCTGGATGATCCT CCAGCGCGGGATCTCATGCTGGAGTTCTTCGCCCACCCCAACTTGTT TATTGCAGCTTATAATGGTTACAAATAAAGCAATAGCATCACAAATTT CACAATAAAGCATTTTTTCACTGCATTCTAGTTGTGGTTTGTCCAA ACTCATCAATCTATCTTATCATGTCTGGATCGCGGCCGCGATCCCGTC GAGAGCTTGGCGTAATCATGGTCATAGCTGTTTCCTGTGTGAAATTGT TATCCGCTCACAATTCCACACAACATACGAGCCGGAAGCATAAAGTG TAAAGCCTGGGGTGCCTAATGAGTGAGCTAACTCACATTAATTGCGTT GCGCTCACTGCCCGCTTTCCAGTCGGGAAACCTGTCGTGCCAGCTGCA TTAATGAATCGGCCAACGCGCGGGGAGAGGCGGTTTGCGTATTGGGC GCTCTTCCGCTCCTCGCTCACTGACTCGCTCGCTCGGTCGTTCGGCT GCGGCGAGCGGTATCAGCTCACTCAAAGGCGGTAATACGGTTATCCA CAGAATCAGGGGATAACGCAGGAAAGAACATGTGAGCAAAAGGCCA GCAAAAGGCCAGGAACCGTAAAAAGGCCGCGTTGCTGGCGTTTTTCC ATAGGCTCCGCCCCCTGACGAGCATCACAAAAATCGACGCTCAAGT CAGAGGTGGCGAAACCCGACAGGACTATAAAGATACCAGGCGTTTCC CCCTGGAAGCTCCCTCGTGCGCTCTCCTGTTCCGACCCTGCCGCTTAC CGGATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTGGCGCTTTCTCA ATGCTCACGCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAA GCTGGGCTGTGCACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTT ATCCGGTAACTATCGTCTTGAGTCCAACCCGGTAAGACACGACTTATC

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FIG. 96E

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GCCACTGGCAGCAGCCACTGGTAACAGGATTAGCAGAGCGAGGTATG TAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGCCTAACTACGGCTAC ACTAGAAGGACAGTATTTGGTATCTGCGCTCTGCTGAAGCCAGTTACC TTCGGAAAAAGAGTTGGTAGCTCTTGATCCGGCAAACAACCACCGC TGGTAGCGGTGGTTTTTTTGTTTGCAAGCAGCAGATTACGCGCAGAAA AAAAGGATCTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGC TCAGTGGAACGAAAACTCACGTTAAGGGATTTTGGTCATGAGATTATC AAAAAGGATCTTCACCTAGATCCTTTTAAATTAAAAATGAAGTTTTAA ATCAATCTAAAGTATATGAGTAAACTTGGTCTGACAGTTACCAATG CTTAATCAGTGAGGCACCTATCTCAGCGATCTGTCTATTTCGTTCATCC ATAGTTGCCTGACTCCCCGTCGTGTAGATAACTACGATACGGGAGGG CTTACCATCTGGCCCCAGTGCTGCAATGATACCGCGAGACCCACGCTC ACCGGCTCCAGATTTATCAGCAATAAACCAGCCAGCCGGAAGGGCCG ATTGTTGCCGGGAAGCTAGAGTAAGTAGTTCGCCAGTTAATAGTTTGC GCAACGTTGTTGCCATTGCTACAGGCATCGTGGTGTCACGCTCGTCGT TTGGTATGGCTTCATTCAGCTCCGGTTCCCAACGATCAAGGCGAGTTA CATGATCCCCCATGTTGTGCAAAAAAGCGGTTAGCTCCTTCGGTCCTC CGATCGTTGTCAGAAGTAAGTTGGCCGCAGTGTTATCACTCATGGTTA TGGCAGCACTGCATAATTCTCTTACTGTCATGCCATCCGTAAGATGCT TTTCTGTGACTGGTGAGTACTCAACCAAGTCATTCTGAGAATAGTGTA TGCGGCGACCGAGTTGCTCTTGCCCGGCGTCAATACGGGATAATACC GCGCCACATAGCAGAACTTTAAAAGTGCTCATCATTGGAAAACGTTCT TCGGGGCGAAAACTCTCAAGGATCTTACCGCTGTTGAGATCCAGTTCG ATGTAACCCACTCGTGCACCCAACTGATCTTCAGCATCTTTTACTTTCA CCAGCGTTTCTGGGTGAGCAAAACAGGAAGGCAAAATGCCGCAAAA AAGGGAATAAGGGCGACACGGAAATGTTGAATACTCATACTCTTCCT TTTTCAATATTATTGAAGCATTTATCAGGGTTATTGTCTCATGAGCGG ATACATATTGAATGTATTTAGAAAAATAAACAAATAGGGGTTCCGC GCACATTTCCCCGAAAAGTGCCACCT

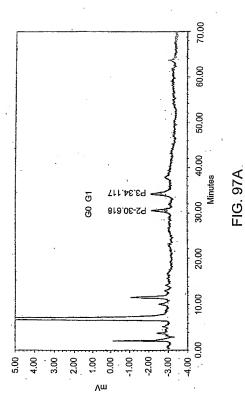
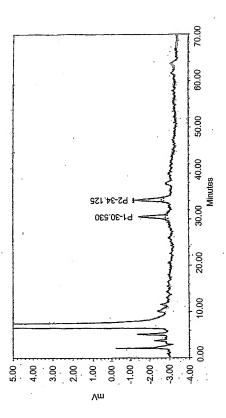
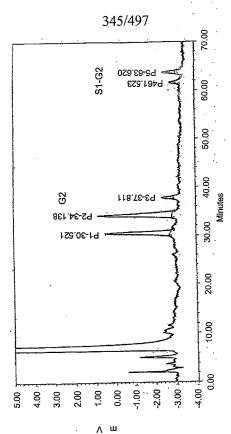


FIG. 97B







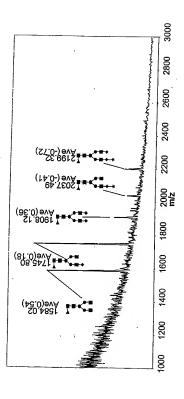


FIG. 98A



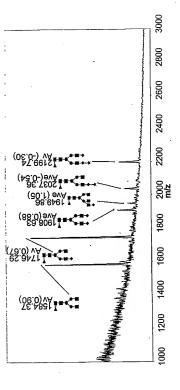


FIG. 98B

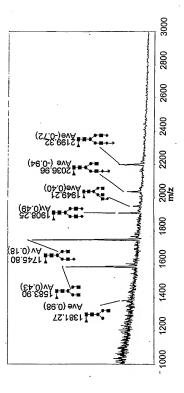
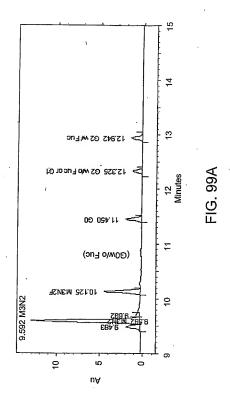
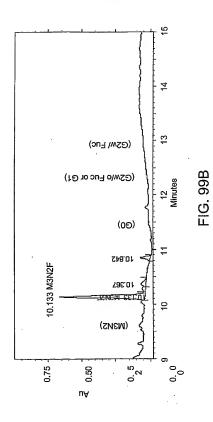
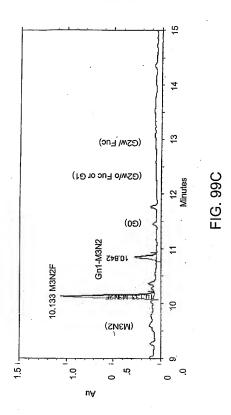


FIG. 98C

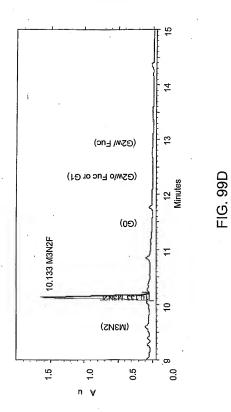
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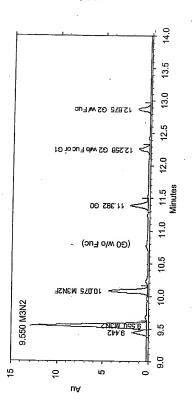
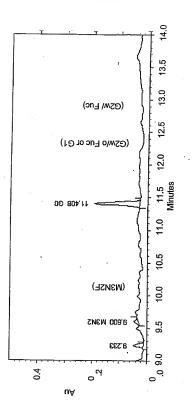
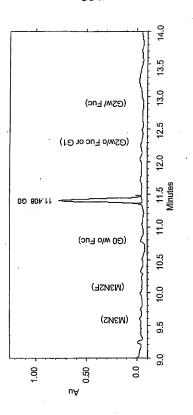


FIG. 100A

FIG. 100B





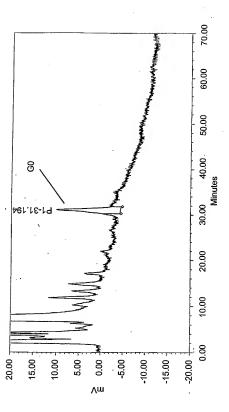


FIG. 101A

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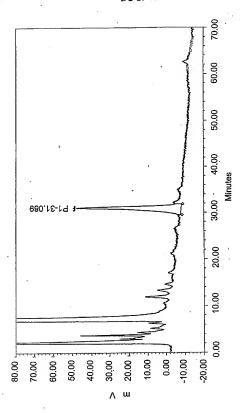
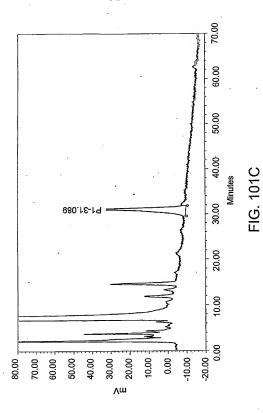


FIG. 101B



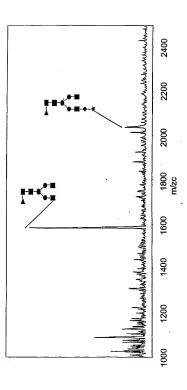
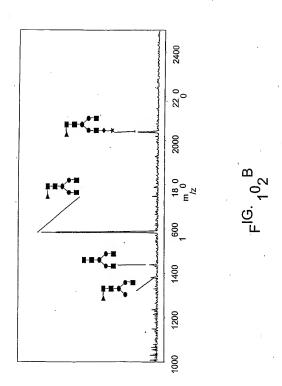


FIG. 102A

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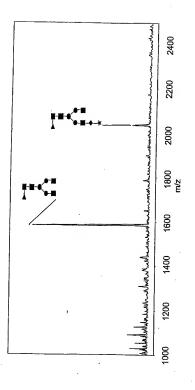


FIG. 102C

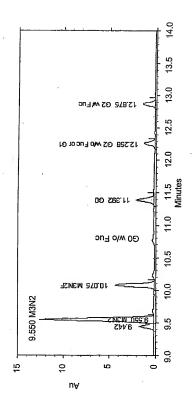
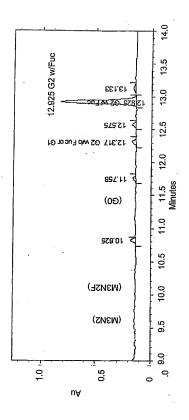
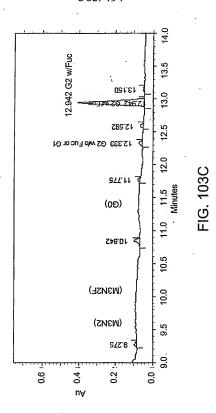


FIG. 103B





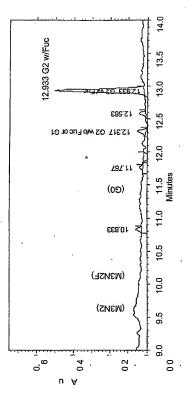


FIG. 103D

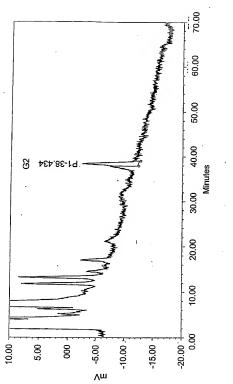
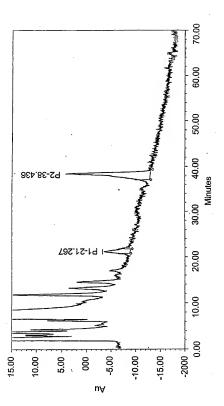
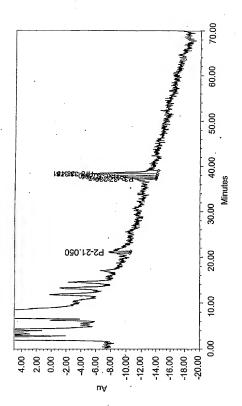


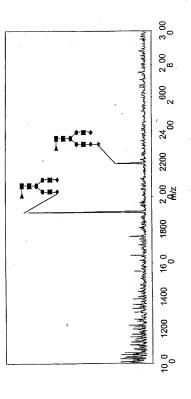
FIG. 104A











-1G. 105A

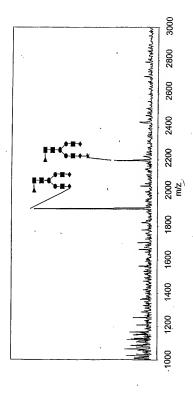


FIG. 105B

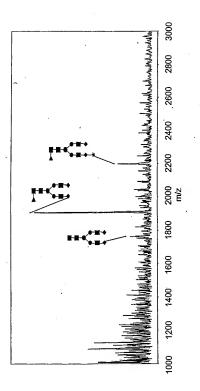
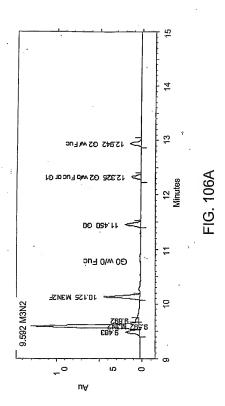
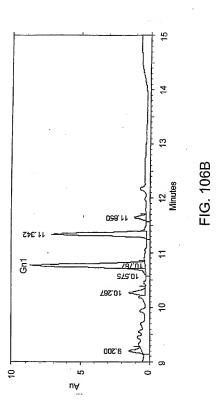
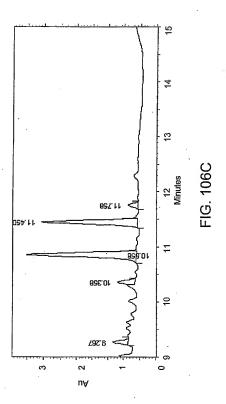
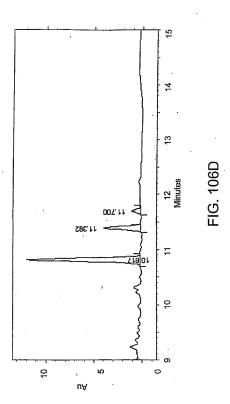


FIG. 105C









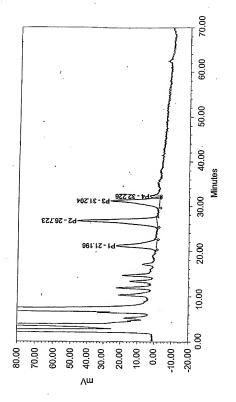
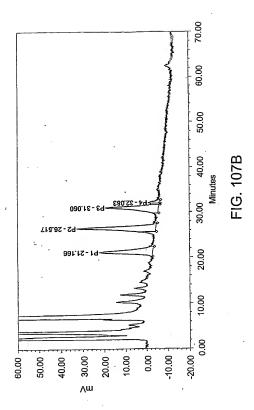
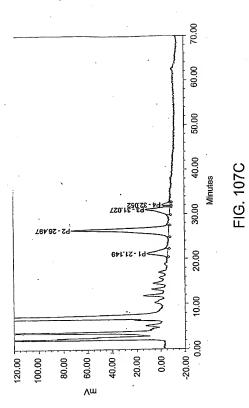
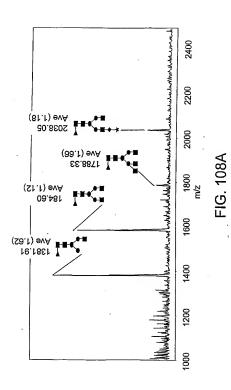


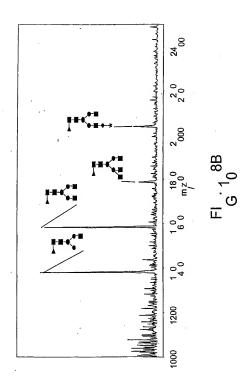
FIG. 107A

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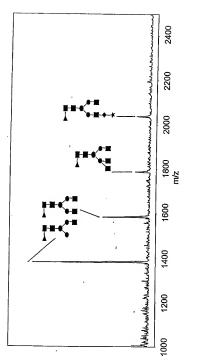
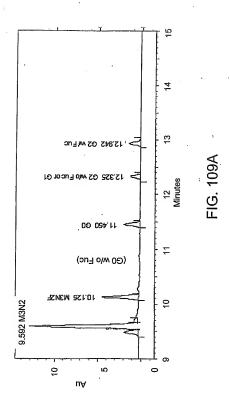
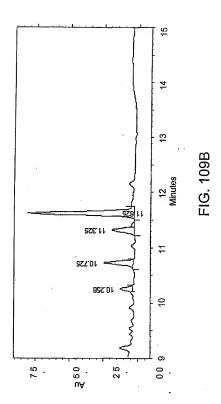
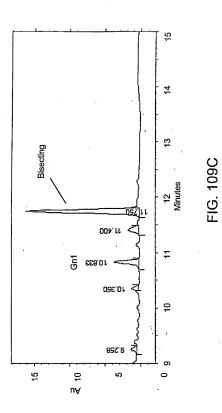
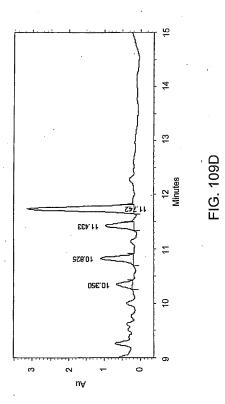


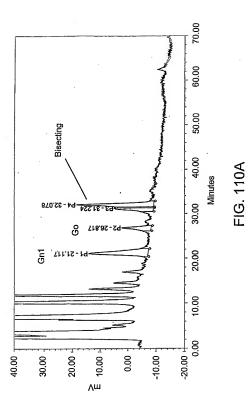
FIG. 108C

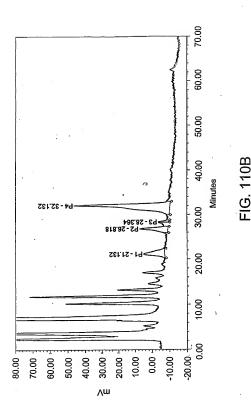


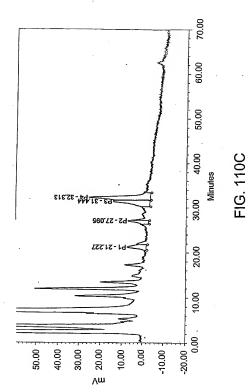












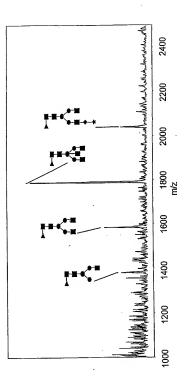


FIG. 111A

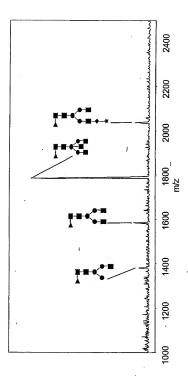
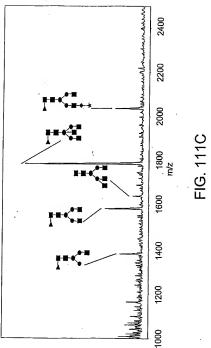
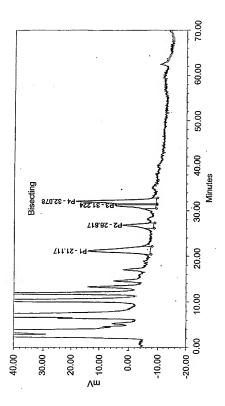


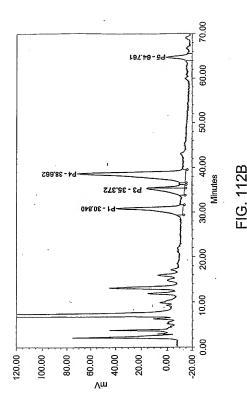
FIG. 111B

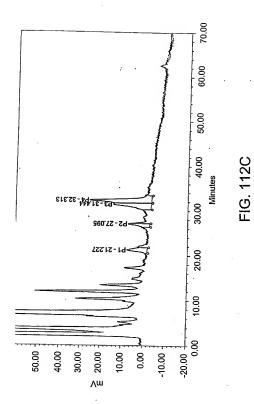


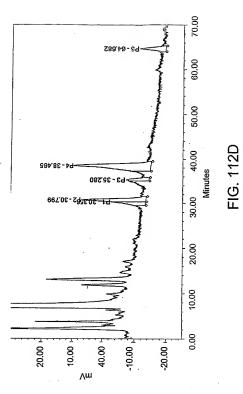




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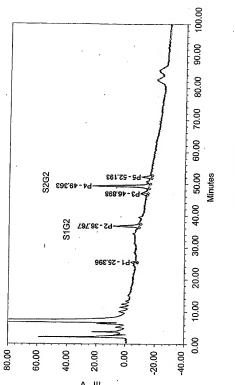
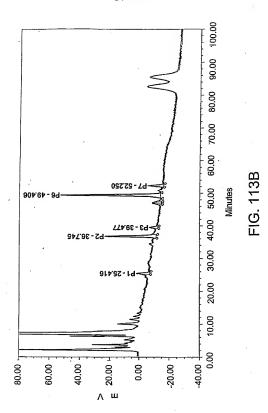
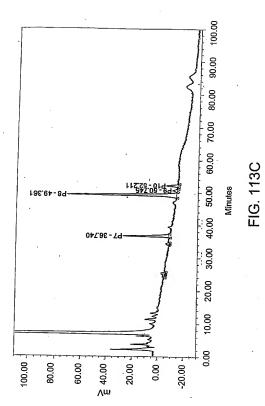
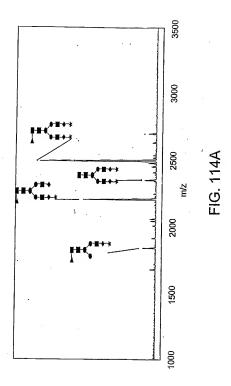


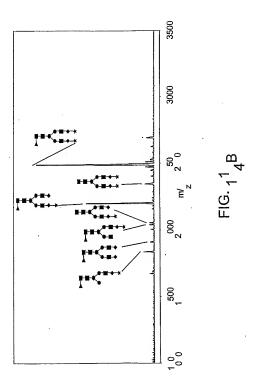
FIG. 113A



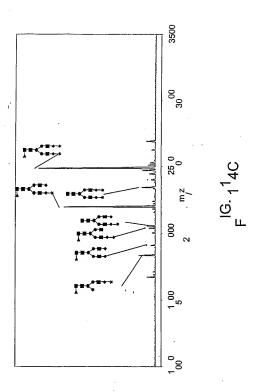




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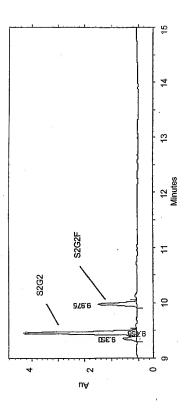
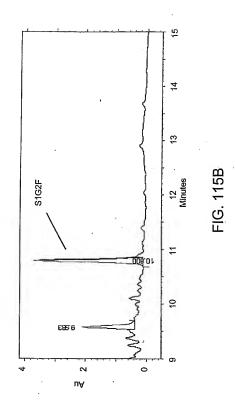
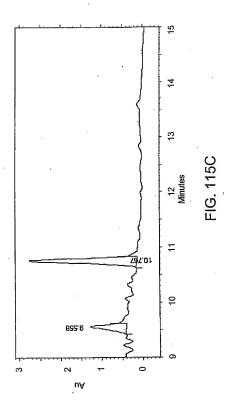
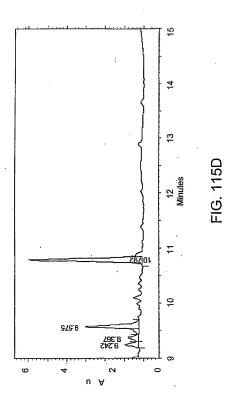


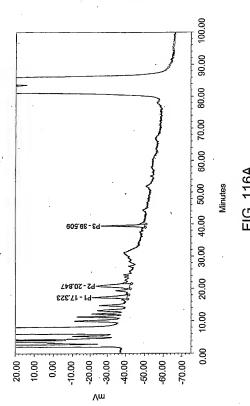
FIG. 115A

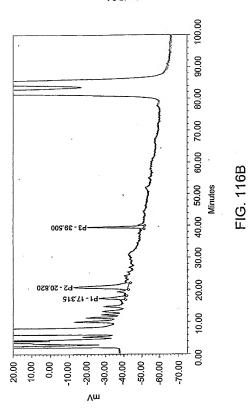


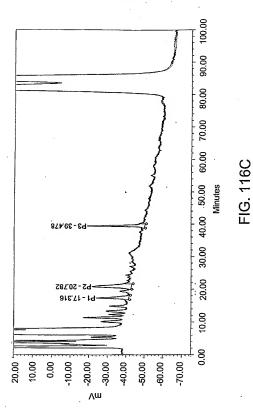


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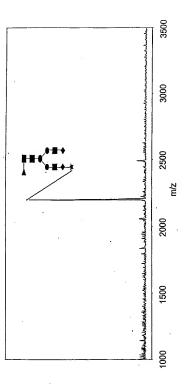




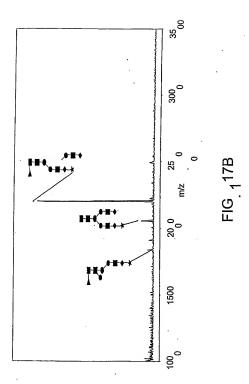




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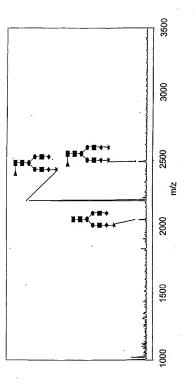


FIG. 117C

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	DEAE				
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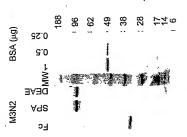


FIG. 118D

FIG. 118C

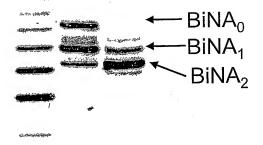
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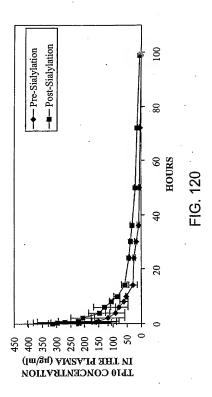
PCT/US2004/011494

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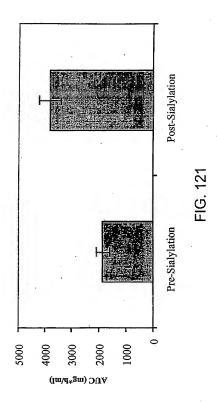


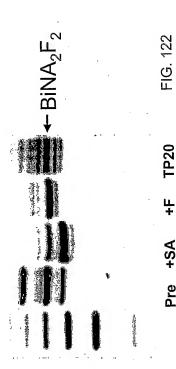
Pre Post

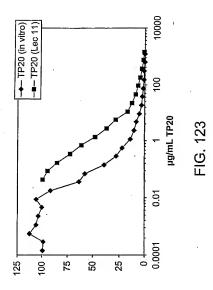
FIG. 119



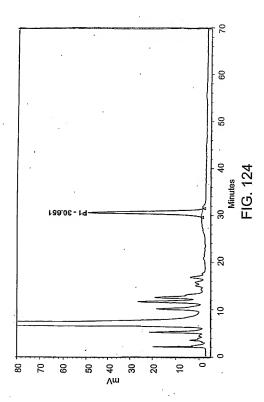
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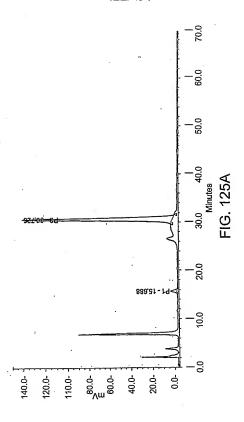




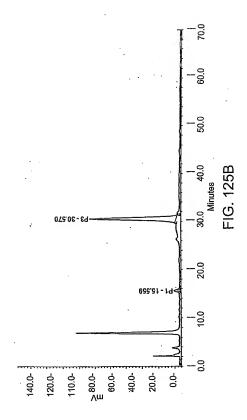


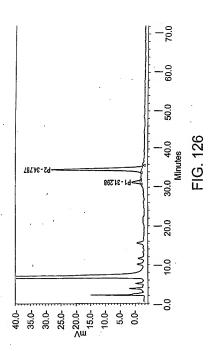
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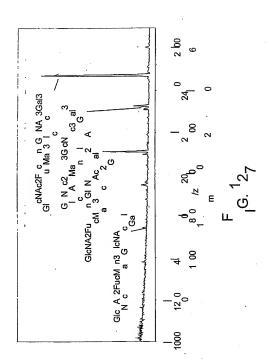




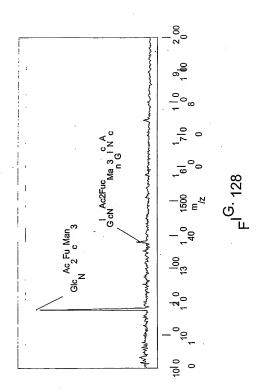
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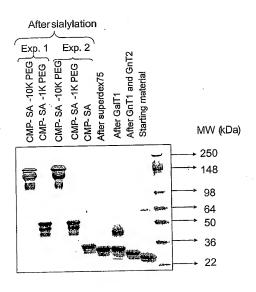
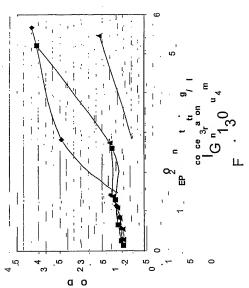
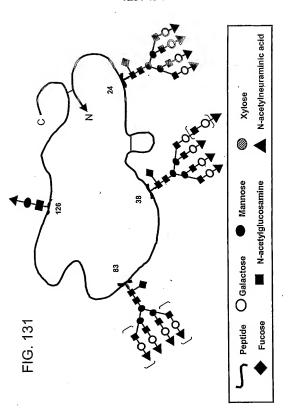


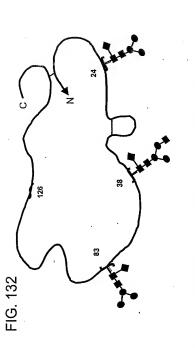
FIG. 129



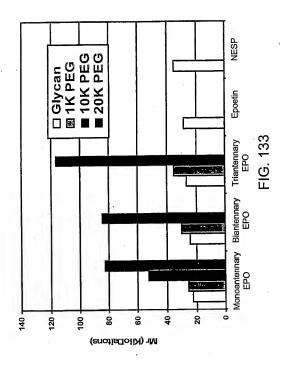


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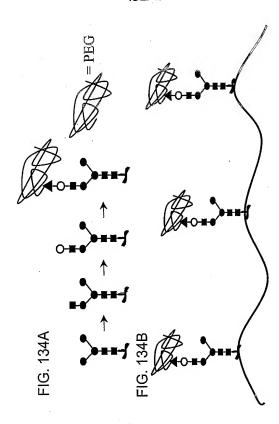




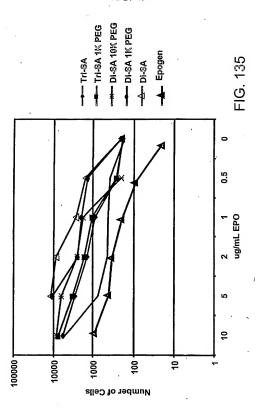


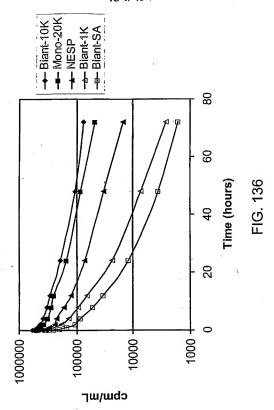


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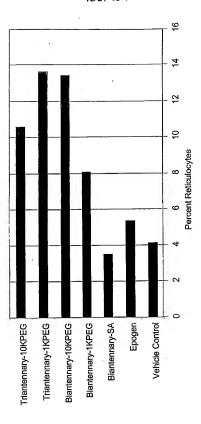


FIG. 137

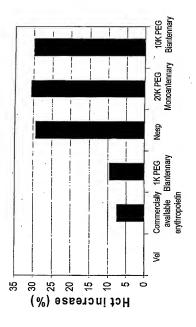
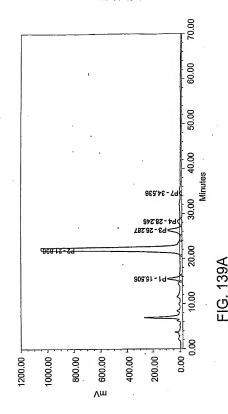
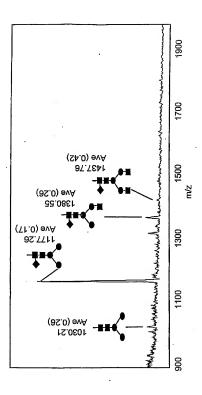
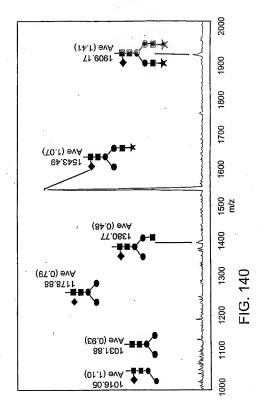


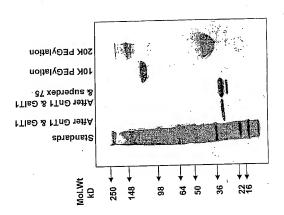
FIG. 138





IG. 139B





=1G. 14′

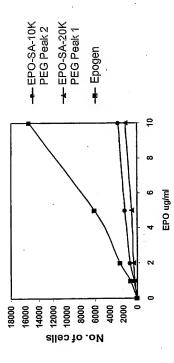


FIG. 142

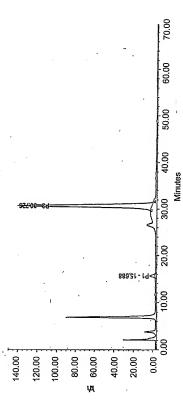


FIG. 143A

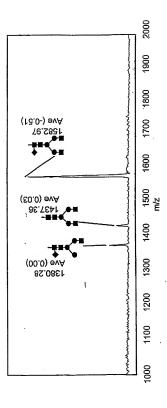
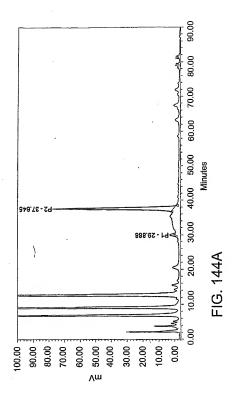


FIG. 143B

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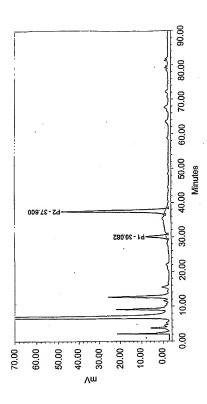
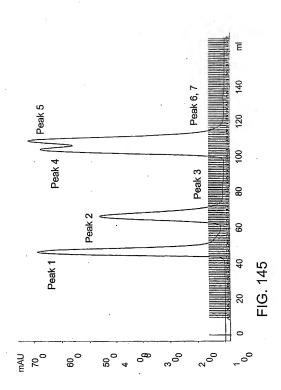
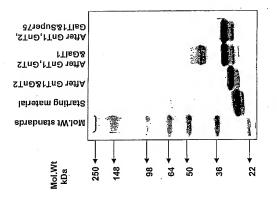
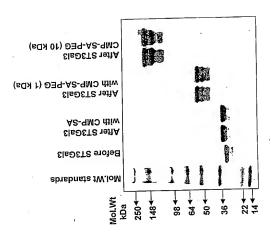


FIG. 144B

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=₁G 147



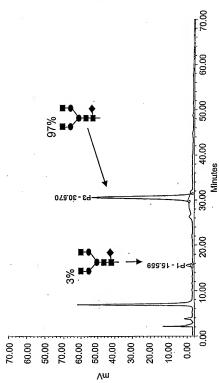
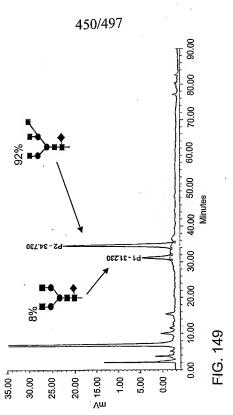
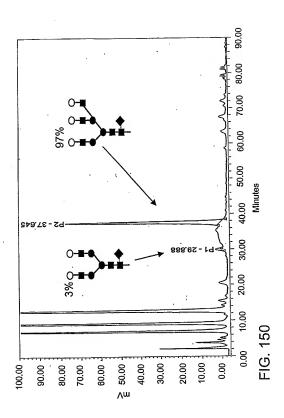
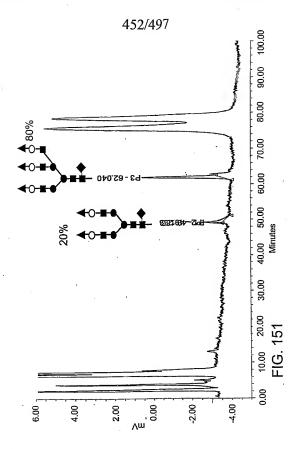


FIG. 148







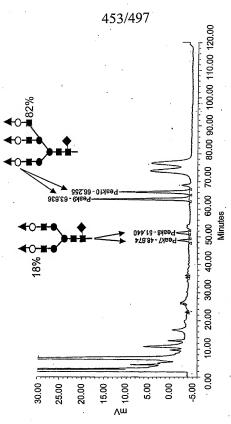


FIG. 152

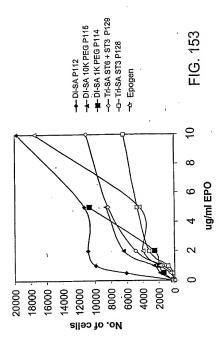




FIG. 154

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FIG. 155

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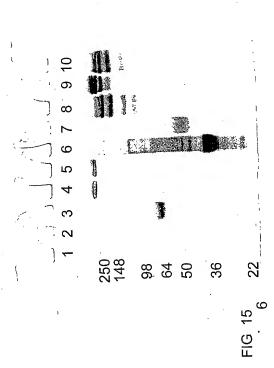
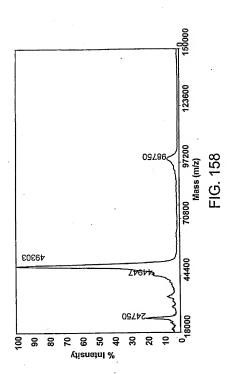
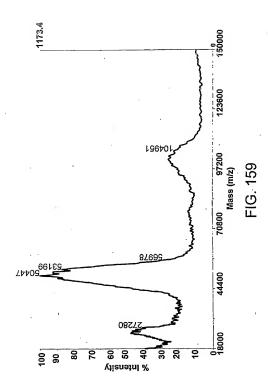


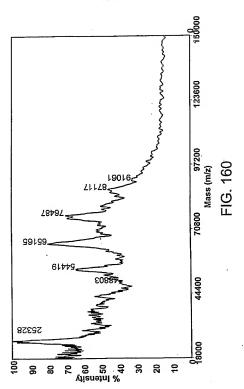


FIG. 157









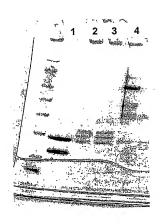


FIG. 161



FIG. 162



FIG. 163

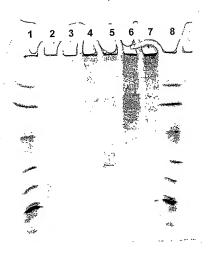


FIG. 164

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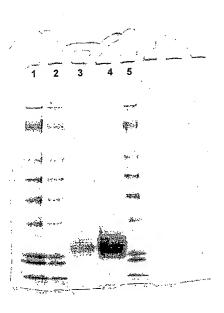


FIG. 165



FIG. 166

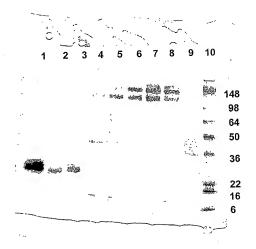


FIG. 167

WO 2004/099231 PCT/US2004/011494

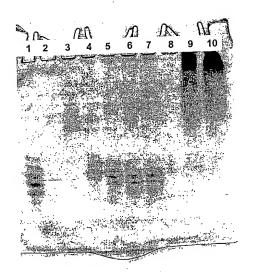
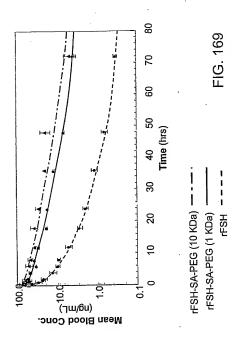
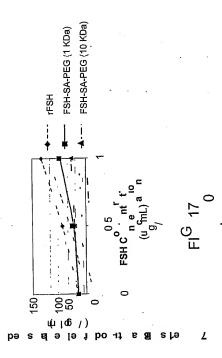
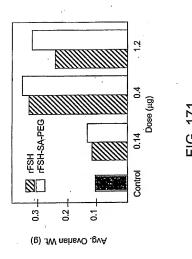


FIG. 168

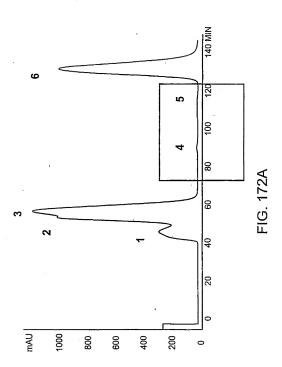


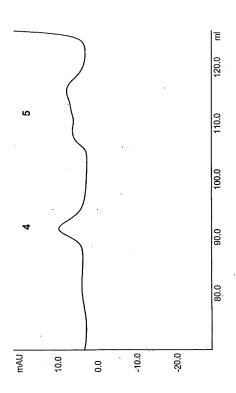


472/497

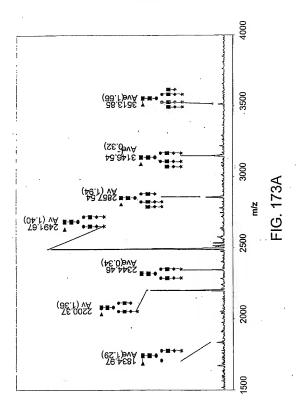


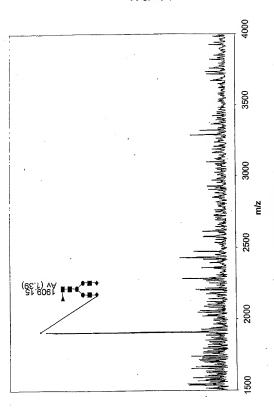
473/497





IG. 172B





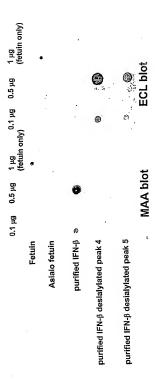
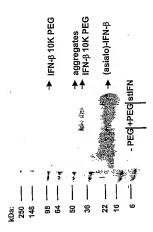
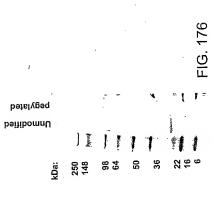
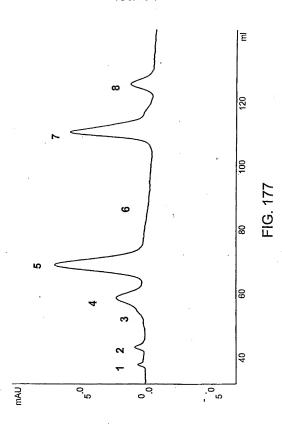


FIG. 174

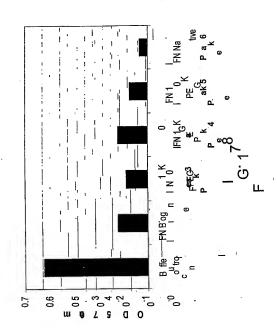




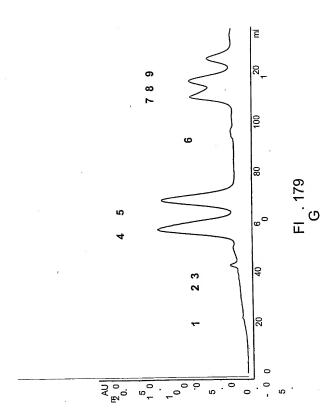
480/497

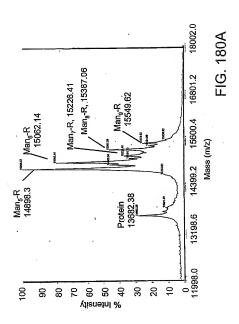


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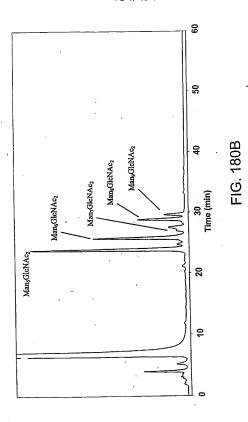


482/497

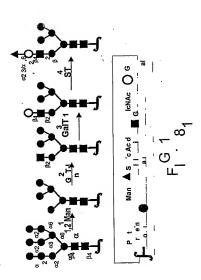




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485/497



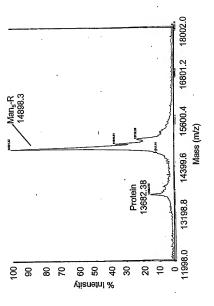
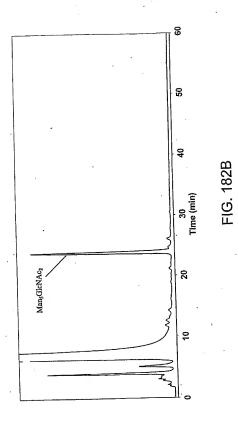
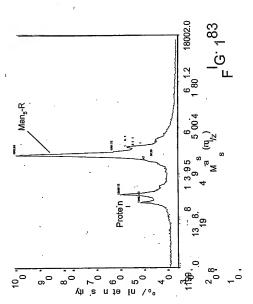
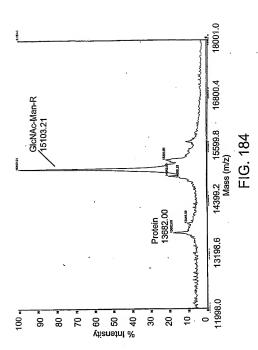


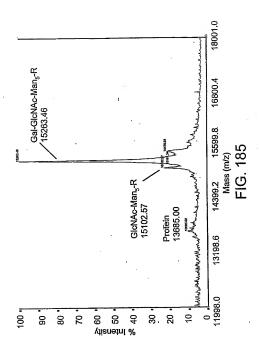
FIG. 182A

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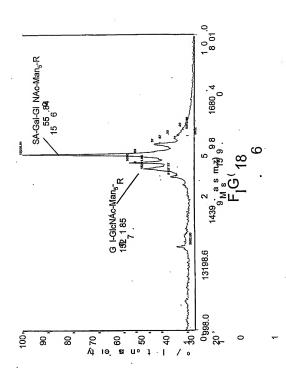








491/497



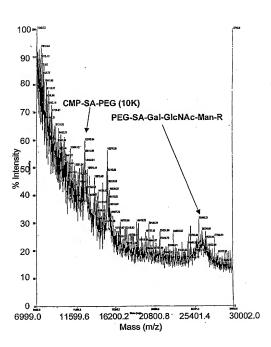


FIG. 187A

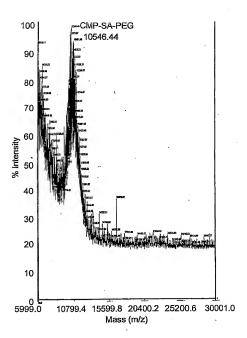
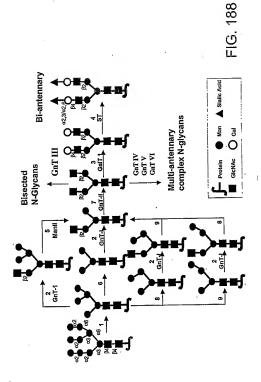
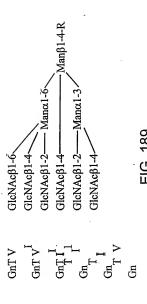


FIG. 187B

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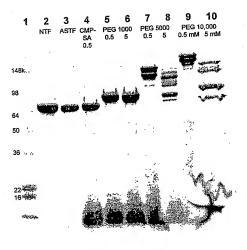


FIG. 190



FIG. 191

- <110> Neose Technologies, Inc.
 - DeFrees, Shawn Zopf, David
 - Bayer, Robert Hakes, David
 - Chen, Xi Bowe, Caryne
- <120> GLYCOPEGYLATION METHODS AND PROTEINS/PEPTIDES PRODUCED BY THE METHODS
- <130> 040853-01-5051WO
- <150> US 60/328,523
- <151> 2001-10-10
- <150> US 60/334,233
- <151> 2001-11-28
- <150> US 60/334,301
- <151> 2001-11-28
 - <150> US 60/344,692
 - <151> 2001-10-19
 - <150> US 60/387,292
 - <151> 2002-06-07
 - <150> US 60/391,777
 - <151> 2002-06-25
 - <150> US 60/396,594.
 - <151> 2002-07-17
 - <150> US 60/404,249 <151> 2002-08-16
 - <150> US 60/407,527
 - <151> 2002-08-28
 - <150> PCT/US02/32263
 - <151> 2002-10-09
 - <150> US 10/360,779
 - <151> 2003-02-19
 - <150> US 10/360,770
 - <151> 2003-01-06
 - <150> US 10/287,994
 - <151> 2002-11-05
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ctgagcaget geeceageea ggeeetgeag etggeagget gettgageea acteeatage 240

ggccttttcc tctaccaggg gctcctgcag gccctggaag ggatctcccc cgagttgggt 300

cecacettgg acacactgca getggacgte gecgaetttg ecaceaccat etggeageag

atggaagaac tgggaatggc ccctgccctg cagcccaccc agggtgccat gccggccttc 420

gcctctgctt tccagcgccg ggcaggaggg gtcctggttg cctcccatct gcagagcttc 480

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Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln 20 25 30

Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val

Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys 50 60

Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser 65 70 . 75 80

Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser 85 90 95

Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp 100 105

Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro 11.5 120 125

Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe

Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe

Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 165 170

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taggatatgt aaatagatac acagtgtata tgtgattaaa atataatggg agattcaatc

agaaaaaagt ttctaaaaag gctctggggt aaaagaggaa ggaaacaata atgaaaaaaa 300

tgtggtgaga aaaacagctg aaaacccatg taaagagtgt ataaagaaag caaaaagaga 360

agtagaaagt aacacagggg catttggaaa atgtaaacga gtatgttccc tatttaaggc

taggcacaaa gcaaggtott cagagaacot ggagcotaag gtttaggotc acccatttca 480

accagtotag cagcatotgo aacatotaca atggcottga cotttgottt actggtggco 540

ctcctggtgc tcagctgcaa gtcaagctgc tctgtgggct gtgatctgcc tcaaacccac 600

agcctgggta gcaggaggac cttgatgctc ctggcacaga tgaggagaat ctctcttttc

toctgottga aggacagaca tgactttgga tttccccagg aggagtttgg caaccagttc 720

caaaaggctg aaaccatccc tgtcctccat gagatgatcc agcagatott caatctcttc 780

agcacaaagg actcatctgc tgcttgggat gagaccctcc tagacaaatt ctacactgaa 840

ctotaccago agotgaatga cotggaagoo tgtgtgatac agggggtggg ggtgacagag 900

actococtga tgaaggagga otocattotg gotgtgagga aatacttoca aagaatcact 960

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ctggttcaac atggaaatga ttttcattga ttcgtatgcc agctcacctt tttatgatct 1140

gccatttcaa agactcatgt ttctgctatg accatgacac gatttaaatc ttttcaaatg 1200

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ttataaaaca acttattttt gttoatatta tgtcatgtgc acctttgcac agtggttaat 1380

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taaaaataaa ctttotgtaa accaagttgt atgttgtact caagataaca gggtgaacct 1620

aacaaataca attotgotot ottgtgtatt tgatttttgt atgaaaaaaa otaaaaatgg 1680

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Lys Ser Ser Cys Ser Val Gly Cys Asp Leu Pro Gln Thr His Ser Leu 20 25 30

Gly Ser Arg Arg Thr Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser 35 40 45

Leu Phe Ser Cys Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu 50 60

Glu Phe Gly Asn Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His 65 70 75 80

4

W(S±u) 2004. • Met	/09923 'Fle	G1n	Gln 85	Пе	Phe	Asn	Leu	Phe 90	Sex	Thr	Lys	Asp	PCT Ser 95	/US2004/011494 Ser
Ala	Ala	Trp	Asp 100	Glu	Thx	Leu	Leu	Asp 105	Lys	Phe	Tyr	Thr	Glu 110	Leu	Tyr
Gln	Gln	Leu 115	Asn	Asp	Leu	Glu	Ala 120	Сув	Val	Ile	Gln	Gly 125	Val	Gly	Val
Thr	Glu 130	Thr	Pro	Leu	Met	Lys 135	Glu	Asp	Ser	Ile	Leu 140	Ala	Val	Arg	Lys
Tyr 145	Phe	Gln	Arg	Ile	Thr 150	Leu	Tyr	Leu	Lуs	Glu 155	Lys	Lys	Tyr	Ser	Pro 160
Cys	Ala	Trp	Glu	Val 165	Val	Arg	Ala	Glu	Ile 170	Met	Arg	Ser	Phe	Ser 175	Leu
Ser	Thr	Asn	Leu 180	Gln	Glu	Ser	Leu	Arg 185	Ser	ГÀЗ	Glu				
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tc:		gct	acaa	cttg	ct t	ggat	tcct	a ca	aaga	agca	gca	attt	tca	gtgt	cagaag
ct (ctgt	ggc	aatt	gaat	gg g	aggo	ttga	a ta	ttgc	ctca	agg	acag	gat	gaac	tttgac
ate 24	catg	agg	agat	taag	ca g	ctgo	agca	ıg tt	ccag	aagg	agg	acgo	cgc	attg	raccato
ta 30		tgc	tcca	gaac	at c	tttg	ctat	t tt	caga	caag	att	cato	tag	cact	ggctgg
aa 36		cta	ttgt	tgag	aa c	ctcc	tggc	t aa	tgtc	tato	ato	agat	aaa	ccat	ctgaag
ac 42		tgg	aaga	aaaa	ct g	gaga	aaga	a ga	tttt	acca	ggg	gaaa	act	cato	jagcagt
ct 48		ctga	aaag	atat	ta t	ggga	ıggat	t ot	gcat	tacc	tga	aggo	caa	ggaç	gtacagt
ca 54	ctgto 0	ject	ggac	cata	igt c	agaç	rtgga	a at	ccta	agga	act	ttta	ctt	catt	aacaga
ct 60		ggtt	acct	ccga	aa c	tgaa	gato	et co	tago	ctgt	cc	etct	ggga	ctg	gacaatt
gc 66		agca	ttct	tcaa	cc a	agcaç	gatgo	st gt	ttaa	gtga	a cto	gatg	gcta	atgt	tactgca

WO 2004/099231 aatgaaagga cactagaaga ttttgaaatt tttattaaat tatgagttat 720										at t	PCT/US2004/011494 ttttatttat						
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	Thr	Thr	Ala	Leu 20	Ser	Met	Ser	Tyr	Asn 25	Leu	Leu	Gly	Phe	Leu 30	Gln	Arg	
	Ser	Ser	Asn 35	Phe	Gln	Cys	Gln	Lys 40	Leu	Leu	Trp	Gln	Leu 45	Asn	Gly	Arg	
	Leu	Glu 50	Tyr	Cys	Leu	Lys	Asp 55	Arg	Met	Asn	Phe	Asp 60	Ile	Pro	Glu	Glu	
	Ile 65	Lys	Gln	Leu	Gln	Gln 70	Phe	G1n	Lys	Glu	Asp 75	Ala	Ala	Leu	Thr	Ile 80	
	Tyr	Glu	Met	Leu	Gln 85	Asn	Ile	Phe	Ala	Ile 90	Phe	Arg	Gln	Asp	Ser 95	Ser	
	Ser	Thr	Gly	Trp	Asn	Glu	Thr	Ile	Val 105	Glu	Asn	Leu	Leu	Ala 110	Asn	Val	
	Tyr	His	Gln 115	Ile	Asn	His	Leu	Lys 120	Thr	Val	Leu	Glu	Glu 125	Lys	Leu	Glu	
	Lys	Glu 130	Asp	Phe	Thr	Arg	Gly 135	Lys	Leu	Met	Ser	Ser 140	Leu	His	Leu	Lys	
	Arg 145	Tyr	Tyr	Gly	Arg	Ile 150	Leu	His	Tyr	Leu	Lys 155	Ala	Lys	Glu	Tyr	Ser 160	
		_			m1	-1 -	**- 1	7	17-1	G1 ₁₁	Tla	T.011	Ara	Asn	Phe	Tvr	

His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Pne 165 170 175

Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn 180

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gcgttcctgg aggagctgcg gccgggctcc ctggagaggg agtgcaagga ggagcagtgc

tccttcgagg aggcccggga gatcttcaag gacgcggaga ggacgaagct gttctggatt 240

tottacagtg atggggacca gtgtgcctca agtccatgcc agaatggggg ctcctgcaag 300

gaccagetee agtectatat etgettetge etceetgeet tegagggeeg gaactgtgag 360

acgcacaagg atgaccagct gatetgtgtg aacgagaacg geggetgtga geagtactgc 420

agtgaccaca cgggcaccaa gcgctcctgt cggtgccacg aggggtactc tctgctggca 480

gacggggtgt cctgcacacc cacagttgaa tatccatgtg gaaaaatacc tattctagaa

aaaagaaatg ccagcaaacc ccaaggccga attgtggggg gcaaggtgtg ccccaaaggg 600

gagtgtccat ggcaggtcct gttgttggtg aatggagctc agttgtgtgg ggggaccctg

atcaacacca totgggtggt ctccgcggcc cactgtttcg acaaaatcaa gaactggagg 720

aacctgatcg cggtgctggg cgagcacgac ctcagcgagc acgacgggga tgagcagagc 780 .

cggcgggtgg cgcaggtcat catccccagc acgtacgtcc cgggcaccac caaccacgac $840\,$

ategogetge teegeetgea ceagecegtg gteeteactg accatgtggt geecetetge 900

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atcacggagt acatgttotg tgccggctac tcggatggca gcaaggactc ctgcaagggg

gacagtggag geccacatge cacceactae eggggeaegt ggtacetgae gggeategte 1200

agetggggce agggetgcgc aacegtggge caetttgggg tgtacaccag ggteteccag 1260

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7

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Leu His Arg Arg Arg Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro

Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu

Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile

Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly

Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro

Ala Phe Glu Gly Arg Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile

Cys Val Asn Glu Asn Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr

Gly Thr Lys Arg Ser Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala 155

Asp Gly Val Ser Cys Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile

Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val

Gly Gly Lys Val Cys Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu 195

Leu Val Asn Gly Ala Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile

Trp Val Val Ser Ala Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg 225

Asn Leu Ile Ala Val Leu Gly Glu His Asp Leu Ser Glu His Asp Gly 250

Asp Glu Gln Ser Arg Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr

Val Pro Gly Thr Thr Asn His Asp Ile Ala Leu Leu Arg Leu His Gln 280 285

8

Pro Val Val Leu Thr Asp His Val Val Pro Leu Cys Leu Pro Glu Arg 290 295 300

Thr Phe Ser Glu Arg Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser 305 \$310\$

Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met 325 330 335

Val Leu Asn Val Pro Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser 340 .

Arg Lys Val Gly Asp Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala 355 365

Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly 370 375 380

Pro His Ala Thr His Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val 385 390 395

Ser Trp Gly Gln Gly Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr 405 410 415

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9

WO 2004/099231				PCT/	US2004/011494
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Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys 50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Pro Arg Glu Val Phe Glu Asn 65 70 75 80

Thr Glu Lys Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln 85 90 90

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile 100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys 115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe 130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly 145 \$150\$

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe 165 170 . 175

Pro Cys Gly Arg Val Ser Val Ser Gln Thr Ser Lys Leu Thr Arg Ala 180 185 190

Glu Ala Val Phe Pro Asp Val Asp Tyr Val Asn Pro Thr Glu Ala Glu 195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Gly Thr Gln Ser Phe Asn Asp Phe 210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp 225 230 230 235

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile $245~\cdot~\cdot~250~$

Val Asn Glu Lys Trp Ile Val Thr Ala Ala Ris Cys Val Glu Thr Gly 260 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu 275 280 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ala Ile Ile Pro His His 290 295 300

Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu 305 \$310\$

Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys 325 330 335

Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly 340 345

Tyr Val Ser Gly Trp Ala Arg Val Phe His Lys Gly Arg Ser Ala Leu 355 366

Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu 370 380 .

Arg Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe 385 390 395

His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His $405 \hspace{1.5cm} 410 \hspace{1.5cm} 415 \hspace{1.5cm}$

Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp 420 425 430

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ttettetecce ageogggtge cecaataett cagtgeatgg getgetgett etetagagea 180

tatcccactc cactaaggtc caagaagacg atgttggtcc aaaagaacgt cacctcagag 240

tocacttgot gtgtagotaa atcatataac agggtoacag taatgggggg tttcaaagtg 300

gagaaccaca cggcgtgcca ctgcagtact tgttattatc acaaatctta aatgttttac 360

caagtgotgt cttgatgact gctgattttc tggaatggaa aattaagttg tttagtgttt 420

atggetttgt gagataaaac teteetttte ettaccatac caetttgaca egetteaagg $480\,$

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Leu Arg Ser Lys Lys Thr Met Leu Val Gln Lys Asn Val Thr Ser Glu 65 70 80

Ser Thr Cys Cys Val Ala Lys Ser Tyr Asn Arg Val Thr Val Met Gly 85 90 95

Gly Phe Lys Val Glu Asn His Thr Ala Cys His Cys Ser Thr Cys Tyr 100 105

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atcaacacca cttggtgtgc tggctactgc tacaccaggg atctggtgta taaggaccca $180\,$

gccaggccca aaatccagaa aacatgtacc ttcaaggaac tggtatatga aacagtgaga $240\,$

gtgcccggct gtgctcacca tgcagattcc ttgtatacat acccagtggc cacccagtgt $300\,$

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Glu Glu Cys Arg Phe Cys Ile Ser Ile Asn Thr Thr Trp Cys Ala Gly 35 40 45

Tyr Cys Tyr Thr Arg Asp Leu Val Tyr Lys Asp Pro Ala Arg Pro Lys 50 60

Ile Gln Lys Thr Cys Thr Phe Lys Glu Leu Val Tyr Glu Thr Val Arg 65 70 80

Val Pro Gly Cys Ala His His Ala Asp Ser Leu Tyr Thr Tyr Pro Val 85 90 . 95

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Glu

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gococoggtg tggtoacoog gogogococa ggtogotgag ggacocoggo caggogoga 180

gatgggggtg cacgaatgte etgeetgget gtggettete etgteeetge tgtegeteee 240

totgggcctc coagtoctgg gogccccacc acgcctcatc tgtgacagcc gagtcctgga 300

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PCT/US2004/011494 WO 2004/099231

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Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu

Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg 70

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PCT/US2004/011494
WO 2004/099231
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     Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly
                                 120
     Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Arg Ala Gln Lys Glu
                             135
     Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile
     Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu
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Thr Ala Ala Glu Met Asn Glu Thr Val Glu Val Ile Ser Glu Met Phe

Asp Leu Gln Glu Pro Thr Cys Leu Gln Thr Arg Leu Glu Leu Tyr Lys

Gln Gly Leu Arg Gly Ser Leu Thr Lys Leu Lys Gly Pro Leu Thr Met

Met Ala Ser His Tyr Lys Gln His Cys Pro Pro Thr Pro Glu Thr Ser

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tattoggtaa ctgacttgaa tgtccaacgc aaagcaatac atgaactcat ccaagtgatg 420

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<212> PRT <213> Homo sapiens

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Gly Thr Leu Phe Leu Gly Ile Leu Lys Asn Trp Lys Glu Glu Ser Asp

Arg Lys Ile Met Gln Ser Gln Ile Val Ser Phe Tyr Phe Lys Leu Phe

Lys Asn Phe Lys Asp Asp Gln Ser Ile Gln Lys Ser Val Glu Thr Ile

Lys Glu Asp Met Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg 105 110

Asp Asp Phe Glu Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val 120

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Ile Ala Thr Ala Phe Ala Met Leu Ser Leu Gly Thr Lys Ala Asp Thr

His Asp Glu Ile Leu Glu Gly Leu Asn Phe Asn Leu Thr Glu Ile Pro

Glu Ala Gln Ile His Glu Gly Phe Gln Glu Leu Leu Arg Thr Leu Asn

Gln Pro Asp Ser Gln Leu Gln Leu Thr Thr Gly Asn Gly Leu Phe Leu 130

Ser Glu Gly Leu Lys Leu Val Asp Lys Phe Leu Glu Asp Val Lys Lys 155 150

Leu Tyr His Ser Glu Ala Phe Thr Val Asn Phe Gly Asp Thr Glu Glu

Ala Lys Lys Gln Ile Asn Asp Tyr Val Glu Lys Gly Thr Gln Gly Lys

Ile Val Asp Leu Val Lys Glu Leu Asp Arg Asp Thr Val Phe Ala Leu

Val Asn Tyr Ile Phe Phe Lys Gly Lys Trp Glu Arg Pro Phe Glu Val 215

Lys Asp Thr Glu Glu Glu Asp Phe His Val Asp Gln Val Thr Thr Val 230

Lys Val Pro Met Met Lys Arg Leu Gly Met Phe Asn Ile Gln His Cys 255

Lys Lys Leu Ser Ser Trp Val Leu Leu Met Lys Tyr Leu Gly Asn Ala 265

Thr Ala Ile Phe Phe Leu Pro Asp Glu Gly Lys Leu Gln His Leu Glu

Asn Glu Leu Thr His Asp Ile Ile Thr Lys Phe Leu Glu Asn Glu Asp

Arg Arg Ser Ala Ser Leu His Leu Pro Lys Leu Ser Ile Thr Gly Thr 315

Tyr Asp Leu Lys Ser Val Leu Gly Gln Leu Gly Ile Thr Lys Val Phe 325 330

Ser Asn Gly Ala Asp Leu Ser Gly Val Thr Glu Glu Ala Pro Leu Lys 345 340

Leu Ser Lys Ala Val His Lys Ala Val Leu Thr Ile Asp Glu Lys Gly 355 360 365

Thr Glu Ala Ala Gly Ala Met Phe Leu Glu Ala Ile Pro Met Ser Ile 370 375 380

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Gly Tyr Ser Ser Val Val Cys Val Cys Asn Ala Thr Tyr Cys Asp Ser 50 60

Phe Asp Pro Pro Thr Phe Pro Ala Leu Gly Thr Phe Ser Arg Tyr Glu 65 70 75 80

Ser Thr Arg Ser Gly Arg Arg Met Glu Leu Ser Met Gly Pro Ile Gln 85 90 95

Ala Asn His Thr Gly Thr Gly Leu Leu Thr Leu Gln Pro Glu Gln
100 105 110

Lys Phe Gln Lys Val Lys Gly Phe Gly Gly Ala Met Thr Asp Ala Ala 115 120 125

Ala Leu Asn Ile Leu Ala Leu Ser Pro Pro Ala Gln Asn Leu Leu Leu 130 135 140

Lys Ser Tyr Phe Ser Glu Glu Gly Ile Gly Tyr Asn Ile Ile Arg Val 145 \$150\$

Pro Met Ala Ser Cys Asp Phe Ser Ile Arg Thr Tyr Thr Tyr Ala Asp 165 170 175

Thr Pro Asp Asp Phe Gln Leu His Asn Phe Ser Leu Pro Glu Glu Asp

Thr Lys Leu Lys Ile Pro Leu Ile His Arg Ala Leu Gln Leu Ala Gln 195 200 205

Arg Pro Val Ser Leu Leu Ala Ser Pro Trp Thr Ser Pro Thr Trp Leu 210 215 220

Lys Thr Asn Gly Ala Val Asn Gly Lys Gly Ser Leu Lys Gly Gln Pro 225 230 235

Gly Asp Ile Tyr His Gln Thr Trp Ala Arg Tyr Phe Val Lys Phe Leu 245 250 255

Asp Ala Tyr Ala Glu His Lys Leu Gln Phe Trp Ala Val Thr Ala Glu $260 \hspace{1cm} 265 \hspace{1cm} 265 \hspace{1cm} 270 \hspace{1cm}$

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Asp Asp Gln Arg Leu Leu Leu Pro His Trp Ala Lys Val Val Leu Thr

Asp Pro Glu Ala Ala Lys Tyr Val His Gly Ile Ala Val His Trp Tyr 340

Leu Asp Phe Leu Ala Pro Ala Lys Ala Thr Leu Gly Glu Thr His Arg

Leu Phe Pro Asn Thr Met Leu Phe Ala Ser Glu Ala Cys Val Gly Ser 375

Lys Phe Trp Glu Gln Ser Val Arg Leu Gly Ser Trp Asp Arg Gly Met 395

Gln Tyr Ser His Ser Ile Ile Thr Asn Leu Leu Tyr His Val Val Gly

Trp Thr Asp Trp Asn Leu Ala Leu Asn Pro Glu Gly Gly Pro Asn Trp 425 420

Val Arg Asn Phe Val Asp Ser Pro Ile Ile Val Asp Ile Thr Lys Asp 440 445

Thr Phe Tyr Lys Gln Pro Met Phe Tyr His Leu Gly His Phe Ser Lys 455

Phe Ile Pro Glu Gly Ser Gln Arg Val Gly Leu Val Ala Ser Gln Lys 475 465

Asn Asp Leu Asp Ala Val Ala Leu Met His Pro Asp Gly Ser Ala Val 490

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Ile Tyr Gln Gln His Gln Ser Trp Leu Arg Pro Val Leu Arg Ser Asn 50 55 60

Arg Val Glu Tyr Cys Trp Cys Asn Ser Gly Arg Ala Gln Cys His Ser 65 70 75 80

Val Pro Val Lys Ser Cys Ser Glu Pro Arg Cys Phe Asn Gly Gly Thr 85 90

Cys Gln Gln Ala Leu Tyr Phe Ser Asp Phe Val Cys Gln Cys Pro Glu 100 105 110

Gly Phe Ala Gly Lys Cys Cys Glu Ile Asp Thr Arg Ala Thr Cys Tyr 115 120 125

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Gly Ala Glu Cys Thr Asn Trp Asn Ser Ser Ala Leu Ala Gln Lys Pro 145 150 160

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Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln

Ala Glu Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser 105

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser

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Phe	Leu 290		Gly	His	Thr	Phe 295	Leu	Val	Arg	Asn	His 300	Arg	Gln	Ala	Ser
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			Gln	325					330					333	
			Glu 340					345					350		
		355					360					303			
	370)	Ser			375					380				
Pr 38		Phe	Ile	Gln	11e 390	Arg	Ser	Val	Ala	Lys 395	Lys	His	Pro	Lys	Thr 400
			туг	405					410)				415	'
			420)				425					430		Asn
		43	5				440					445	,		Met
	45	0				455	5				460	,			Glu
Se 46		y Il	e Lev	ı Gly	Pro 470	Leu	Leu	туз	Gl	7 Glu 475	ı Val	L Gly	y Asp	Th:	Leu 480
Le	u Il	e Il	e Phe	485	a Asn	Glr	n Ala	s Sex	490	g Pro	Ту	c Ası	n Ile	49!	r Pro

His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe 515 $$ 525

Lys	Tyr 530	Lys	Trp	Thr	Val	Thr 535	Val	Glu	Asp	Gly	Pro 540	Thr	Lys	Ser	Asp	
Pro 545	Arg	Cys	Leu	Thr	Arg 550	Tyr	Tyr	Ser	Ser	Phe 555	Val	Asn	Met	Glu	Arg 560	
Asp	Leu	Ala	Ser	Gly 565	Leu	Ile	Gly	Pro	Leu 570	Leu	Ile	Cys	Tyr	Lys 575	Glu	
Ser	۷al	Asp	Gln 580	Arg	Gly	Asn	Gln	Ile 585	Met	Ser	Asp	Lys	Arg 590	Asn	Val	
Ile	Leu	Phe 595	Ser	Val	Phe	Asp	Glu 600	Asn	Arg	Ser	Trp	Tyr 605	Leu	Thr	Glu	
Asn	Ile 610	Gln	Arg	Phe	Leu	Pro 615	Asn	Pro	Ala	Gly	Val 620	Gln	Leu	Glu	Asp	
Pro 625	Glu	Phe	Gl.n	Ala	Ser 630	Asn	Ile	Met	His	Ser 635	Ile	Asn	Gly	Tyr	Val 640	
Phe	Asp	Ser	Leu	Gln 645	Leu	Ser	Val	Cys	Leu 650	His	Glu	Val	Ala	Tyr 655	Trp	
Tyr	Ile	Leu	Ser 660	Ile	Gly	Ala	Gln	Thr 665	Asp	Phe	Leu	Ser	Val 670	Phe	Phe	
Ser	Gly	Tyr 675		Phe	Lys	His	Lys 680	Met	Val.	Tyr	Glu	Asp 685	Thr	Leu	Thr	
Leu	Phe 690	Pro	Phe	Ser	Gly	Glu 695	Thr	Val	Phe	Met	Ser 700	Met	Glu	Asn	Pro	
Gly 705	Leu	Trp	Ile	Leu	Gly 710	Сув	His	Asn	Ser	Asp 715	Phe	Arg	Asn	Arç	720	
				725					/30					750		
Tyr	Tyr	Glu	Asp 740	Ser	Tyr	Glu	. Asp	745	Ser	Ala	Tyr	Leu	750	Ser	Lys	
Asn	Asn	Ala 755	Ile	Glu	Pro	Arg	Ser 760	Phe	Ser	Gln	Asn	Ser 765	Arq	His	arg	
Ser	7hr	Arg	Gln	Lys	Glr	775	Asr	n Ala	Thr	Thr	780	Pro	Gl:	Ası	a Asp	
11e 785		Lys	Thr	Asp	790	Trp	Phe	e Ala	His	795	Thr	Pro) Met	Pro	800 800	
Ile	Glr	a Asr	val	Ser 805	Sea	Ser	: Ası	p Lev	ьец 810	Met	: Leu	Let	ı Ar	9 Gl: 81	n Ser 5	
Pro	Thi	r Pro	His 820	Gly	Lei	sez	Le	825	Asp	Lev	ı Glr	Gl:	1 Al. 83	а Б у	s Tyr	
Glu	Thi	Phe 835		Asp	As)	Pro	Se:	r Pro	Gl:	y Ala	ı Ile	84!	p Se: 5	r As	n Asn	

		4/099													I/US2004
Ser	Leu 850	Ser	Glu	Met	Thr	His 855	Phe	Arg	Pro	Gln	ьеи 860	His	His	ser	GTÀ
Asp 865	Met	Val	Phe	Thr	Pro 870	Glu	Ser	Gly	Leu	Gln 875	Leu	Arg	Leu	Asn	Glu 880
Ьуs	Leu	Gly	Thr	Thr 885	Ala	Ala	Thr	Glu	Lev 890	Lys	Lys	Leu	Asp	Phe 895	Lys
Val	Ser	Ser	Thr 900		Asn	Asn	Leu	Ile 905	Ser	Thr	Ile	Pro	Ser 910	Asp	Asn
Leu	Ala	Ala 915		Thr	Asp	Asn	Thr 920	Ser	Ser	Lev	Gly	Pro 925	Pro	Ser	Met
Pro	Val 930		Tyr	Asp	Ser	Gln 935	Lev	Asp	Thi	Thi	940	ı Phe	Gly	Lys	Lys
Ser 945		Pro	Leu	Thr	Glu 950	Ser	Gl	Gl ₃	/ Pro	95	se:	r Leu	Ser	Glu	Glu 960
Asn	Asn	Asp	Ser	Lys 965	Leu	Leu	Gli	ı Se	Gl;	y Lev	ı Me	t Asn	Ser	Gln 975	Glu
Ser	Ser	Trp	Gly 980	ьуs	Asn	Val	Sea	Se:	r Th	r Gl	ı Se	r Gly	990	Leu	Phe
Lys	Gly	Lys 995	Arg	Ala	His	Gly	Pro 10	D A	la L	eu L	eu T	hr Ly 10	rs P 105	sp A	sn Ala
Leu	Phe 101		s Va	al Se	r Il	e Se	r :	Leu :	Leu	Lys	Thr	Asn 1020	Lys	Thr	Ser
Asr	Asr 102		er Al	La Th	r As	n Ai	g 30	Lys	Thr	His	Ile	Asp 1035	Gly	Pro	Ser
Leu	Let 104		Le G	Lu As	n Se		0 045	Ser	Val	Trp	Gln	Asn 1050	Ile	Leu	Glu
Sei	Asp 105		nr G	lu Pl	e Ly	/s L	/s 060	Val	Thr	Pro	Leu	Ile 1065	His	Asp	Arg
Met	Let 101		et A	sp L	ys As	sn A	la 075	Thr	Ala	Leu	Arg	Leu 1080	Asn	His	Met
Se	r Ası		ys T	hr T	nr Se	er S	er 090	Lys	Asn	Met	Glu	Met 1095	Val	Gln	Gln
Ly	s Ly:	s G	lu G	ly P	ro I	le P	ro 105	Pro	Asp	Ala	Gln	Asn 1110	Pro	Asp	Met
Se	r Ph		he L	ys M	et L	eu P	he 120	Leu	Pro	Glu	Ser	Ala 1125	Arg	Trp	Ile

1115 Gln Arg Thr His Gly Lys Asn Ser Leu Asn Ser Gly Gln Gly Pro 1130 1135 Ser Pro Lys Gln Leu Val Ser Leu Gly Pro Glu Lys Ser Val Glu 1155 1150 1145

Gly Gln Asn Phe Leu Ser Glu Lys Asn Lys Val Val Val Gly Lys

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	1160					1165					1170			
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Ser	Ser 1190	Arg	Asn	Leu	Phe	Leu 1195	Thr	Asn	Leu	Asp	Asn 1200	Leu	His	Glu
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Lys	Lys 1220	Glu	Thr	Leu	Ile	Gln 1225	G1u	Asn	Val	Val	Leu 1230	Pro	Gln	Ile
His	Thr 1235	Val	Thr	Gly	Thr	Lys 1240	Asn	Phe	Met	Ьуз	Asn 1245	Leu	Phe	Leu
Leu	Ser 1250	Thr	Arg	Gln	Asn	Val 1255	Glu	G1y	Ser	Tyr	Asp 1260	Gly	Ala	Tyr
Ala	Pro 1265	Val	Leu	Gln	Asp	Phe 1270	Arg	Ser	Leu	Asn	Asp 1275	Ser	Thr	Asn
	Thr 1280	-	-			1285					Lys 1290		Glu	
G1u	Asn 1295					1300					1305			
-	Tyr 1310					1315					Thr 1320			
Asn	Phe 1325	Val	Thr	Gln	Arg	Ser 1330	Ľуs	Arg	Ala	Leu	Lys 1335	Gln	Phe	Arg
Leu	Pro 1340					1345					Ile 1350			Asp
Asp	Thr 1355					1360					His 1365			
	Thr 1370					1375					Glu 1380			
	Thr 1385					1390					1395	,		
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Ser	Phe 1415		Ser	Ile	Arg	Pro 1420		Туг	Leu	Thr	Arg 1425	Val	Leu	Phe
	1430	ı				1435	i				1440)	-	Lys
_	Ser 1445	,				1450)				1455)		
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Leu	Pro 1505	Lys	Thr	Ser	Gly	Lys 1510	Val	Glu	Leu	Leu	Pro 1515	Lys	Val	His	
Ile	Tyr 1520	Gln	Ьys	Asp	Leu	Phe 1525	Pro	Thr	Glu	Thr	Ser 1530	Asn	Gly	Ser	
Pro	Gly 1535	His	Leu	Asp	Leu	Val 1540	Glu	Gly	Ser	Leu	Leu 1545	Gln	Gly	Thr	
Glu	Gly 1550	Ala	Ile	Lys	Trp	Asn 1555	Glu	Ala	Asn	Arg	Pro 1560	Gly	ГÀЗ	Val	
	Phe 1565					1570					1575				
	Leu 1580					1585					1590				
	Pro 1595					1600					1000				
	Ala 1610					1615					1020				
	Ser 1625					1630					1.020				
	Glu 1640					1645					1650				
	Cys 1655					1660					T002				
	Thr 1670	•				1675	•				1000	•	_	Tyr	
	Asp 1685					1690)				1695	,			
	1700)				1705	•				1/10	,			
Thr	Arg 1715	5				1720)				1/2	,			
	Met 1730)				1735	5				1740)			
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41

Asp Gly Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu 1760 1760 1770

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His	Leu 1775	Gly	Leu	Leu	GTĀ	ero 1780	Tyr	11e	Arg	Ala	GIU 1785	vaı	GIU	ASP
Asn	Ile 1790	Met	Val	Thr	Phe	Arg 1795	Asn	Gln	Ala	Ser	Arg 1800	Pro	Tyr	Ser
Phe	Tyr 1805	Ser	Ser	Leu	Ile	Ser 1810	Tyr	Glu	Glu	Asp	Gln 1815	Arg	Gln	Gly
Ala	Glu 1820	Pro	Arg	Lys	Asn	Phe 1825	Val	Lys	Pro	Asn	Glu 1830	Thr	Lys	Thr
Tyr	Phe 1835	Trp	Lys	Val	Gln	His 1840	His	Met	Ala	Pro	Thr 1845	Lys	Asp	Glu'
Phe	Asp 1850	Cys	Lys	Ala	Trp	Ala 1855	Tyr	Phe	Ser	Asp	Val 1860	Asp	Leu	Glu
Lys	Asp 1865	Val	His	Ser	Gly	Leu 1870	Ile	Gly	Pro	Leu	Leu 1875	Val	Cys	His
Thr	Asn 1880		Leu	Asn	Pro	Ala 1885	His	Gly	Arg	Gln	Val 1890	Thr	Val	Gln
Glu	Phe 1895		Leu	Phe	Phe	Thr 1900	Ile	Phe	Asp	Glu	Thr 1905	Ьуs	Ser	Trp
Tyr	Phe 1910		Glu	Asn	Met	Glu 1915	Arg	Asn	Cys	Arg	Ala 1920	Pro	Cys	Asn
Ile	Gln 1925	Met	Glu	Asp	Pro	Thr 1930	Phe	Lys	Glu	Asn	Tyr 1935	Arg	Phe	His
Ala	Ile 1940	Asn	Gly	Tyr	Ile	Met 1945	Asp	Thr	Leu	Pro	Gly 1950	Leu	Val	Met
Ala	Gln 1955	Asp	Gln	Arg	Ile	Arg 1960	Trp	Tyr	Leu	Leu	Ser 1965	Met	Gly	Ser
Asn	Glu 1970		Ile	His	Ser	Ile 1975	His	Phe	Ser	Gly	His 1980		Phe	Thr
Val	Arg 1985		Lys	Glu	Glu	Tyr 1990		Met	Ala	Leu	Tyr 1995	Asn	Lev	Tyr
Pro	Gly 2000		Phe	Glu	Thr	Val 2005		Met	Leu	Pro	Ser 2010	Lys	Ala	Gly
Ile	Trp 2015		Val	Glu	Cys	Leu 2020	Ile	Gly	Glu	His	Leu 2025	His	Ala	Gly
Met	Ser 2030		Leu	Phe	Leu	Val 2035	Tyr	Ser	Asn	Lys	Cys 2040		Thr	Pro
Leu	Gly 2045		Ala	Ser	Gly	His 2050		Arg	Asp	Phe	Gln 2055		Thr	Ala
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Lys	Thr 2105	Gln	Gly	Ala	Arg	Gln 2110	Lys	Phe	Ser	Ser	Leu 2115	Tyr	Ile	Ser
Gln	Phe 2120	Ile	Ile	Met	Tyr	Ser 2125	Leu	Asp	Gly	Lys	Lys 2130	Trp	Gln	Thr
Tyr	Arg 2135	Gly	Asn	Ser	Thr	Gly 2140	Thr	Leu	Met	Val	Phe 2145	Phe	Gly	Asn
Val	Asp 2150	Ser	ser	Gly	Ile	Lys 2155	His	Asn	Ile	Phe	Asn 2160	Pro	Pro	Ile
Ile	Ala 2165	Arg	Tyr	Ile	Arg	Leu 2170	His	Pro	Thr	His	Tyr 2175	Ser	Ile	Arg
Ser	Thr 2180		Arg	Met	Glu	Leu 2185	Met	Gly	Cys	Asp	Leu 2190	Asn	Ser	Сув
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Ile	Thr 2210		Ser	Ser	Tyr	Phe 2215	Thr	Asn	Met	Phe	Ala 2220	Thr	Trp	Ser
_		T	חות	7) ***	Lou	uie	T.en	Gin	Glv	Ara	Ser	Asn	Ala	Trp

Pro Ser Lys Ala Arg Leu His Leu Gin Gly Arg Ser 2235 Asn Ala Trp 2230 230 Rsn Ala Trp 2335 Asn Ala Trp 233 Rsn Ala Trp 233 Rsn

2240 2245 2250

Gln Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln Gly Val Lys

2255 2260 2255 Ser Leu Leu Thr Ser Met Tyr Val Lys Glu Phe Leu Ile Ser Ser

Ser Gln Asp Gly His Gln Trp Thr Leu Phe Phe Gln Asn Gly Lys 2285 2290 2295

Val Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr Pro Val Val 2300 2300

Asn Ser Leu Asp Pro Pro Leu Leu Thr Arg Tyr Leu Arg Ile His 2315 2325

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Thr Ala Gln Met Cys Cys Ser Lys Cys Ser Pro Gly Gln His Ala Lys

Val Phe Cys Thr Lys Thr Ser Asp Thr Val Cys Asp Ser Cys Glu Asp

Ser Thr Tyr Thr Gln Leu Trp Asn Trp Val Pro Glu Cys Leu Ser Cys

Gly Ser Arg Cys Ser Ser Asp Gln Val Glu Thr Gln Ala Cys Thr Arg

Glu Gln Asn Arg Ile Cys Thr Cys Arg Pro Gly Trp Tyr Cys Ala Leu 115

Ser Lys Gln Glu Gly Cys Arg Leu Cys Ala Pro Leu Arg Lys Cys Arg

Pro Gly Phe Gly Val Ala Arg Pro Gly Thr Glu Thr Ser Asp Val Val 145

Cys Lys Pro Cys Ala Pro Gly Thr Phe Ser Asn Thr Thr Ser Ser Thr 165

Asp Ile Cys Arg Pro His Gln Ile Cys Asn Val Val Ala Ile Pro Gly

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Met Ala Pro Gly Ala Val His Leu Pro Gln Pro Val Ser Thr Arg Ser

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Phe Le	eu L	eu	Pro	Met 245	Gly	Pro	Ser	Pro	Pro 250	Ala	Glu	Gly	Ser	Thr 255	Gly	
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Leu Le		1e 75	Ile	Gly	Val	Val	Asn 280	Суѕ	Val	Ile	Met	Thr 285	Gl n	Val	Lys	
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Ala A	sp L	ys	Ala	Arg	Gly 310	Thr	Gln	Gly	Pro	Glu 315	Gln	Gln	His	Leu	Leu 320	
Ile T	hr A	.la	Pro	Ser 325	Ser	Ser	Ser	Ser	Ser 330	Leu	Glu	Ser	Ser	Ala 335	Ser	•
Ala L	eu A	ga	Arg 340	Arg	Ala	Pro	Thr	Arg 345	Asn	Gln	Pro	Gln	Ala 350	Pro	Gly	
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His Trp Cys Asn Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile 50 55 60

Asp Lys Ser Lys Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly 65 70 75 80

Lys Ala Ser Thr Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser 85 · 90 95

Ala Thr Val Leu Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu 100 105 110

Gln Leu Gly Leu Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg

Arg Arg Pro Trp Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln 130 135 140

Glu Cys Met Val His Asp Cys Ala Asp Gly Lys Lys Pro Ser Pro 145 150 160

Pro Glu Glu Leu Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg

Phe Lys Ile Glu Glu Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp 180 \$185\$

Phe Ala Ala Ile Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val 195 205

Cys Gly Gly Ser Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His

Cys Phe Ile Asp Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly

Arg Ser Arg Leu Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val 245 250 255

Glu Asn Leu Ile Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His

His Asn Asp Ile Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys 275 280 285

Ala Gln Pro Ser Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr 290 295 300

Asn Asp Pro Gln Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys 305 310 315

Glu Asn Ser Thr Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val 325 330 335

Val Lys Leu Ile Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly 340 345 350

Ser Glu Val Thr Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys $355 \hspace{1.5cm} 360 \hspace{1.5cm} 365 \hspace{1.5cm}$

Thr Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu 370 375 380

Gln Gly Arg Met Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys 385 390 395

Ala Leu Lys Asp Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu 405 410 415

Pro Trp Ile Arg Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu 420 425 430

<210> 35

<211> 107 <212> PRT

<213> Mus musculus

<400> 35 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala 20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile 35 40 45

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly 50 60

Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

<210> 36 <211> 120

<212> PRT <213> Mus musculus

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 35 40 45

Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val 50 60

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr 65 70 75

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys $85 \hspace{1.5cm} 90 \hspace{1.5cm} 70 \hspace{1.5cm} 10 \hspace{1.5cm}$

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser 115 120

<210> 37

<211> 120 <212> PRT

<213> Mus musculus

 $<\!400>$ 37 Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln 1 1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser 20 25 30

Gly Met Ser Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Ala Leu Glu 35 40 45

Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser 50 60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val 65 70 75 80

Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr 85 90 95

Cys Ala Arg Ser Met Ile Thr Asn Trp Tyr Phe Asp Val Trp Gly Ala

Gly Thr Thr Val Thr Val Ser Ser

<210> 38

<211> 106 <212> PRT

<213> Mus musculus

<400> 38

<400> 38
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val. Thr Ile Thr Cys Lys Cys Gln Leu Ser Val G1y Tyr Met 20 .25

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Trp Ile Tyr

Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser 50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp 65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr 85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys

<210> 39

<211> 1039

<212> DNA

<213> Homo sapiens

<400> 39

tectgracag gragtgrett gaagtgrette tteagagace tttetteata gactactttt 60

ttttctttaa gcagcaaaag gagaaaattg tcatcaaagg atattccaga ttcttgacag 120

cattetegte atetetgagg*acateaceat cateteagga tgaggggeat gaagetgetg

ggggcgctgc tggcactggc ggccctactg cagggggccg tgtccctgaa gatcgcagcc 240

ttcaacatcc agacatttgg ggagaccaag atgtccaatg ccaccctcgt cagctacatt 300

gtgcagatcc tgagccgcta tgacatcgcc ctggtccagg aggtcagaga cagccacctg 360

actgoogtgg ggaagetget ggacaacete aatcaggatg caccagacac etatcactac 420

gtggtcagtg agccactggg acggaacagc tataaggagc gctacctgtt cgtgtacagg

cotgaccagg tgtctgcggt ggacagctac tactacgatg atggctgcga gccctgcggg 540

aacgacacct tcaaccgaga gccagccatt gtcaggttot tctcccggtt cacagaggtc 600

PCT/US2004/011494 WO 2004/099231

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gctctctatg acgtctacct ggatgtccaa gagaaatggg gcttggagga cgtcatgttg

atgggcgact tcaatgcggg ctgcagctat gtgagaccct cccagtggtc atccatccgc

ctgtggacaa gccccacctt ccagtggctg atccccgaca gcgctgacac cacagctaca 840

cccacgcact gtgcctatga caggatcgtg gttgcaggga tgctgctccg aggcgccgtt

gttcccgact cggctcttcc ctttaacttc caggctgcct atggcctgag tgaccaactg

goccaagoca toagtgacca ctatocagtg gaggtgatgo tgaagtgago agoccotoco 1020

cacaccagtt gaactgcag 1039

<210> 40

<211> 282

<212> PRT

<213> Homo sapiens

<400> 40

Met Arg Gly Met Lys Leu Leu Gly Ala Leu Leu Ala Leu Ala Ala Leu

Leu Gln Gly Ala Val Ser Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr

Phe Gly Glu Thr Lys Met Ser Asn Ala Thr Leu Val Ser Tyr Ile Val

Gln Ile Leu Ser Arg Tyr Asp Ile Ala Leu Val Gln Glu Val Arg Asp 55

Ser His Leu Thr Ala Val Gly Lys Leu Leu Asp Asn Leu Asn Gln Asp

Ala Pro Asp Thr Tyr His Tyr Val Val Ser Glu Pro Leu Gly Arg Asn

Ser Tyr Lys Glu Arg Tyr Leu Phe Val Tyr Arg Pro Asp Gln Val Ser

Ala Val Asp Ser Tyr Tyr Tyr Asp Asp Gly Cys Glu Pro Cys Gly Asn 120

Asp Thr Phe Asn Arg Glu Pro Ala Ile Val Arg Phe Phe Ser Arg Phe

Thr Glu Val Arg Glu Phe Ala Ile Val Pro Leu His Ala Ala Pro Gly 160 145 150

Asp Ala Val Ala Glu Ile Asp Ala Leu Tyr Asp Val Tyr Leu Asp Val

Gln Glu Lys Trp Gly Leu Glu Asp Val Met Leu Met Gly Asp Phe Asn

Ala Gly Cys Ser Tyr Val Arg Pro Ser Gln Trp Ser Ser Ile Arg Leu

Trp Thr Ser Pro Thr Phe Gln Trp Leu Ile Pro Asp Ser Ala Asp Thr 210 215 220

Thr Ala Thr Pro Thr His Cys Ala Tyr Asp Arg Ile Val Val Ala Gly 225 230 235 240

Met Leu Leu Arg Gly Ala Val Val Pro Asp Ser Ala Leu Pro Phe Asn 245 250 255

Phe Gln Ala Tyr Gly Leu Ser Asp Gln Leu Ala Gln Ala Ile Ser 260 265 270

Asp His Tyr Pro Val Glu Val Met Leu Lys 275 280

<210> 41

<211> 678 <212> DNA

<213> Mus musculus

<400> 41 gacatetttge tgacteagte tecagecate etgtetgtga gtecaggaga aagagteagt 60

ttotoctgca gggccagtca gttogttggc tcaagcatcc actggtatca gcaaagaaca 120

aatggttctc caaaggcttct cataaagtat gcttctgagt ctatgtctgg gatcccttcc 180

aggtttagtg gcagtggatc agggacagat tttactctta gcatcaacac tgtggagtct 240

gaagatattg cagattatta ctgtcaacaa agtcatagct ggccattcac gttcggctcg 300

gggacaaatt tggaagtaaa agaagtgaag cttgaggagt ctggaggagg cttggtgcaa 360

cotggaggat ccatgaaact ctoctgtgtt gcctctggat tcattttcag taaccactgg 420

atgaactggg teegeeagte teeagagaag gggettgagt gggttgetga aattagatea 480

aaatotatta attotgoaac acattatgog gagtotg
tga aagggaggtt caccatotca $540\,$

agagatgatt ccaaaagtgc tgtctacctg caaatgaccg acttaagaac tgaagacact

ggcgtttatt actgttccag gaattactac ggtagtacct acgactactg gggccaaggc 660

accactctca cagtetec 678

<210> 42

<211> 226 <212> PRT

<213> Mus musculus

<400> 42

Asp Ile Leu Eur Thr Gln Ser Pro Ala Ile Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Phe Val Gly Ser Ser 25 25

Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile

Lys Tyr Ala Ser Glu Ser Met Ser Gly Ile Pro Ser Arg Phe Ser Gly 50 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Thr Val Glu Ser 65 70 75 80

Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Ser His Ser Trp Pro Phe 85 90 95

Thr Phe Gly Ser Gly Thr Asn Leu Glu Val Lys Glu Val Lys Leu Glu 100 \$100\$

Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Met Lys Leu Ser

Cys Val Ala Ser Gly Phe Ile Phe Ser Asn His Trp Met Asn Trp Val

Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val Ala Glu Ile Arg Ser 145 150 155 160

Lys Ser Ile Asn Ser Ala Thr His Tyr Ala Glu Ser Val Lys Gly Arg

Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ala Val Tyr Leu Gln Met 180 . 185

Thr Asp Leu Arg Thr Glu Asp Thr Gly Val Tyr Tyr Cys Ser Arg Asn 195 200 205

Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr

Val Ser 225

<210> 43

<211> 450 <212> DNA

<213> Homo sapiens

<400> 43

getgeateag aagaggeeat caageacate actgteette tgeeatggee etgtggatge 60

gcctcctgcc cctgctggcg ctgctggccc tctggggacc tgacccagcc gcagcctttg

tgaaccaaca cetgtgcggc tcacacctgg tggaagctct ctacctagtg tgcggggaac

gaggettett etacacacec aagaceegee gggaggeaga ggaeetgeag gtggggeagg 240

tggagctggg cgggggccct ggtgcaggca gcctgcagcc cttggccctg gaggggtccc

tgcagaagcg tggcattgtg gaacaatgct gtaccagcat ctgctccctc taccagctgg

agaactactg caactagacg cagecegeag geageceece accegeegee teetgeaceg 420

agagagatgg aataaagccc ttgaaccagc 450

<210> 44

<211> 110

<212> PRT

<213> Homo sapiens

<400> 44

Met Ala Leu Trp Met Arg Leu Leu Pro Leu Leu Ala Leu Leu Ala Leu

Trp Gly Pro Asp Pro Ala Ala Ala Phe Val Asn Gln His Leu Cys Gly

Ser His Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe

Phe Tyr Thr Pro Lys Thr Arg Arg Glu Ala Glu Asp Leu Gln Val Gly

Gln Val Glu Leu Gly Gly Gly Pro Gly Ala Gly Ser Leu Gln Pro Leu 65

Ala Leu Glu Gly Ser Leu Gln Lys Arg Gly Ile Val Glu Gln Cys Cys

Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn 100

<210> 45

<211> 1203 <212> DNA

<213> Hepatitis B virus

<400> 45

atgggaggtt ggtcttccaa acctcgacaa ggcatgggga cgaatctttc tgttcccaat

cetetgggat tetttecega teaceagttg gaccetgegt teggageeaa eceaaacaac 120

ccagattggg acttcaaccc caacaaggat cactggccag aggcaatcaa ggtaggagcg

ggagacttcg ggccagggtt caccccacca cacggcggtc ttttggggtg gagccctcag 240

getcagggca tattgacaac agtgccagca gegectecte etgtttccae caateggcag 300

teaggaagae agectactee cateteteea eetetaagag aeagteatee teaggeeatg 360

cagtggaact ccacaacatt ccaccaagct ctgctagatc ccagagtgag gggcctatat 420

tttcctgctg gtggctccag ttccggaaca gtaaaccotg ttccgactac tgtctcaccc 480

atatcgtcaa tottetegag gaetggggac cetgcaccga acatggagag cacaacatca 540

ggattcctag gaccoctgct cgtgttacag gcggggtttt tcttgttgac aagaatcctc

acaataccac agagtetaga etegtggtgg acttetetea attttetagg gggageacce

acgtgtcotg gocaaaattc gcagtcccca acctccaatc actcaccaac ctcttgtcct 720

ccaatttgto ctggttatcg ctggatgtgt ctgcggcgtt ttatcatatt cctcttcatc 780

ctgctgctat goctcatctt cttgttggtt cttctggact accaaggtat gttgcccgtt 840

tytoctotae ttocaggaac atcaactace ageacgggac catgcaagac etgcacgatt 900

cctgctcaag gaacctctat gtttccctct tgttgctgta caaaaccttc ggacggaaac 960

tgcacttgta ttoccatocc atcatectgg getttogcaa gatteetatg ggagtgggcc 1020

teagteegtt teteetgget eagtttacta gtgccatttg tteagtggtt egeagggett

tcccccactg tttggctttc agttatatgg atgatgtggt attgggggcc aagtctgtac 1140

aacatottga gtocottttt acototatta ccaattttot tttgtotttg ggtatacatt 1200

tga 1203

<210> 46

PCT/US2004/011494 WO 2004/099231

<211> 400

<212> PRT

<213> Hepatitis B virus

Met Gly Gly Trp Ser Ser Lys Pro Arg Gln Gly Met Gly Thr Asn Leu .

Ser Val Pro Asn Pro Leu Gly Phe Phe Pro Asp His Gln Leu Asp Pro

Ala Phe Gly Ala Asn Ser Asn Asn Pro Asp Trp Asp Phe Asn Pro Asn

Lys Asp His Trp Pro Glu Ala Ile Lys Val Gly Ala Gly Asp Phe Gly

Pro Gly Phe Thr Pro Pro His Gly Gly Leu Leu Gly Trp Ser Pro Gln

Ala Gln Gly Ile Leu Thr Thr Val Pro Ala Ala Pro Pro Pro Val Ser

Thr Asn Arg Gln Ser Gly Arg Gln Pro Thr Pro Ile Ser Pro Pro Leu 105

Arg Asp Ser His Pro Gln Ala Met Gln Trp Asn Ser Thr Thr Phe His

Gln Ala Leu Leu Asp Pro Arg Val Arg Gly Leu Tyr Phe Pro Ala Gly

Gly Ser Ser Ser Gly Thr Val Asn Pro Val Pro Thr Thr Val Ser Pro 155

Ile Ser Ser Ile Phe Ser Arg Thr Gly Asp Pro Ala Pro Asn Met Glu 165

Ser Thr Thr Ser Gly Phe Leu Gly Pro Leu Leu Val Leu Gln Ala Gly 185

Phe Phe Leu Leu Thr Arg Ile Leu Thr Ile Pro Gln Ser Leu Asp Ser 205

Trp Trp Thr Ser Leu Asn Phe Leu Gly Gly Ala Pro Thr Cys Pro Gly 210 215

Gln Asn Ser Gln Ser Pro Thr Ser Asn His Ser Pro Thr Ser Cys Pro 235

Pro Ile Cys Pro Gly Tyr Arg Trp Met Cys Leu Arg Arg Phe Ile Ile

Phe Leu Phe Ile Leu Leu Cys Leu Ile Phe Leu Leu Val Leu Leu

Asp Tyr Gln Gly Met Leu Pro Val Cys Pro Leu Leu Pro Gly Thr Ser 280

Thr Thr Ser Thr Gly Pro Cys Lys Thr Cys Thr Ile Pro Ala Gln Gly

Thr Ser Met Phe Pro Ser Cys Cys Cys Thr Lys Pro Ser Asp Gly Asn 305 310 315

Cys Thr Cys Ile Pro Ile Pro Ser Ser Trp Ala Phe Ala Arg Phe Leu 325 330 335

Trp Glu Trp Ala Ser Val Arg Phe Ser Trp Leu Ser Leu Leu Val Pro 340 345 . 350

Phe Val Gln Trp Phe Ala Gly Leu Ser Pro Thr Val Trp Leu Ser Val 355 360 365

Ile Trp Met Met Trp Tyr Trp Gly Pro Ser Leu Tyr Asn Ile Leu Ser 370 380

Pro Phe Leu Pro Leu Pro Ile Phe Phe Cys Leu Trp Val Tyr Ile 385 390 395 400

<210> 47 <211> 799

<212> DNA <213> Homo sapiens

<400> 47

cgaaccactc agggtcctgt ggacagctca cctagctgca atggctacag gctcccggac

gtocotgotc otggottttg gootgototg cotgocotgg ottoaagagg goagtgoott 120

cccaaccatt cccttatcca ggccttttga caacgctatg ctccgcgccc atcgtctgca

ccagctggcc tttgacacct accaggagtt tgaagaagcc tatatcccaa aggaacagaa

gtattcattc ctgcagaacc cccagacctc cctctgtttc tcagagtcta ttccgacacc 300

ctocaacagg gaggaaacac aacagaaatc caacctagag ctgctccgca tctccctgct 360

gotoatocag togtggotgg agdcoqtgoa gttoctcagg agtgtottcg coaacagoot 420 °

ggtgtacggc gcctctgaca gcaacgtcta tgacctccta aaggacctag aggaaggcat 480

ccaaacgctg atggggagge tggaagatgg cagccccgg actgggcaga tettcaagca 540

gacctacage aagttegaca caaacteaca caacgatgae geactactea agaactaegg 600

gotgototac tgottcagga aggacatgga caaggtcgag acattcctgc gcatcgtgca

gtgccgctct gtggagggca gctgtggctt ctagctgccc gggtggcatc cctgtgaccc 720

ctccccagtg cctctcctgg ccctggaagt tgccactcca gtgcccacca gccttgtcct

aataaaatta aqttgcatc

<210> 48

<211> 217 <212> PRT

<213> Homo sapiens

<400> 48

Met Ala Thr Gly Ser Arg Thr Ser Leu Leu Leu Ala Phe Gly Leu Leu 10

Cys Leu Pro Trp Leu Gln Glu Gly Ser Ala Phe Pro Thr Ile Pro Leu

Ser Arg Pro Phe Asp Asn Ala Met Leu Arg Ala His Arg Leu His Gln

Leu Ala Phe Asp Thr Tyr Gln Glu Phe Glu Glu Ala Tyr Ile Pro Lys

Glu Gln Lys Tyr Ser Phe Leu Gln Asn Pro Gln Thr Ser Leu Cys Phe

Ser Glu Ser Ile Pro Thr Pro Ser Asn Arg Glu Glu Thr Gln Gln Lys

Ser Asn Leu Glu Leu Leu Arg Ile Ser Leu Leu Leu Ile Gln Ser Trp 105

Leu Glu Pro Val Gln Phe Leu Arg Ser Val Phe Ala Asn Ser Leu Val 115

Tyr Gly Ala Ser Asp Ser Asn Val Tyr Asp Leu Leu Lys Asp Leu Glu 135

Glu Gly Ile Gln Thr Leu Met Gly Arg Leu Glu Asp Gly Ser Pro Arg

Thr Gly Gln Ile Phe Lys Gln Thr Tyr Ser Lys Phe Asp Thr Asn Ser 170 165

His Asn Asp Asp Ala Leu Leu Lys Asn Tyr Gly Leu Leu Tyr Cys Phe 185

Arg Lys Asp Met Asp Lys Val Glu Thr Phe Leu Arg Ile Val Gln Cys 205 195

Arg Ser Val Glu Gly Ser Cys Gly Phe 215 210

<210> 49

<211> 963 <212> DNA

<213> Homo sapiens

<400> 49

atggagacag acacactect gttatgggtg etgetgetet gggtteeagg trecaetggt 60

gacgtcaggc gagggccccg gagcctgcgg ggcagggacg cgccagcccc cacgccctgc

gtcccggccg agtgcttcga cctgctggtc cgccactgcg tggcctgcgg gctcctgcgc 180

acgccgcggc cgaaaccggc cggggccagc agccctgcgc ccaggacggc gctgcagccg 240

caggagtegg tgggegeggg ggeeggegag geggeggteg acaaaactea cacatgeeca 300

cegtgcccag cacetgaact cetgggggga cegteagtet teetetteee cecaaaacec 360

aaggacaccc tcatgatctc ccggacccct gaggtcacat gcgtggtggt ggacgtgagc 420

cacgaagacc ctgaggtcaa gttcaactgg tacgtggacg gcgtggaggt gcataatgcc 480

aagacaaagc cgcgggagga gcagtacaac agcacgtacc gtgtggtcag cgtcctcacc 540

gtcctgcacc aggactggct gaatggcaag gagtacaagt gcaaggtctc caacaaagcc 600

ctcccagcce ccatcgagaa aaccatctcc aaagccaaag ggcagccccg agaaccacag

gtgtacaccc tgcccccatc ccgggatgag ctgaccaaga accaggtcag cctgacctgc 720

ctggtcaaag gcttctatcc cagcgacatc gccgtggagt gggagagcaa tgggcagccg 780

gagaacaact acaagaccac gcotcocgtg ttggactccg acggeteett etteetetac $840\,$

agcaagctica cogtggacaa gagcaggtgg cagcagggga acgtettete atgeteegtg 900

atgcatgagg ctctgcacaa ccactacacg cagaagagcc tctccctgtc tcccgggaaa 960

tga 963

<210> 50

<211> 320 <212> PRT

<213> Homo sapiens

<400> 50 Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro

Gly Ser Thr Gly Asp Val Arg Arg Gly Pro Arg Ser Leu Arg Gly Arg

20 25 30

Asp Ala Pro Ala Pro Thr Pro Cys Val Pro Ala Glu Cys Phe Asp Leu 35 40 45

Leu Val Arg His Cys Val Ala Cys Gly Leu Leu Arg Thr Pro Arg Pro 50 55 60

Lys Pro Ala Gly Ala Ser Ser Pro Ala Pro Arg Thr Ala Leu Gln Pro 65 70 80

Gln Glu Ser Val Gly Ala Gly Ala Gly Glu Ala Ala Val Asp Lys Thr $85 \hspace{1cm} 90 \hspace{1cm} 95$

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser 100 105 110

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg 115 , 120 125

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro 130 135 140

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala 145 150 150

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val 165 . 170 . 175

Ser Val Leu Thr Val Leu Ris Gln Asp Trp Leu Asn Gly Lys Glu Tyr 180 185 190

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr $195 \hspace{1.5cm} 200 \hspace{1.5cm} 205 \hspace{1.5cm}$

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu 210 215 . 220

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys 225 230 240

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser 245 250 250

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp 260 265

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser 275 280 285

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala 290 295 300

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys 305 310 315 320

<210> 51

<211> 107 <212> PRT

<213> Homo sapiens

<400> 51
Asp Ile Gln Met Thr Gln Thr Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 .10
15

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Asn Asn Tyr 20 25 30 .

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile 35 40 45

Tyr Tyr Thr Ser Thr Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly 50 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro 65 70 75 80

Asp Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp $85 \hspace{1.5cm} 90 \hspace{1.5cm} 95$

Thr Phe Gly Gln Gly Thr Lys Val Glu Val Lys

<210> 52

<211> 107 <212> PRT

<213> Mus musculus

<400> 52

Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly 1 10 15 15 Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Asn Asn Tyr

20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Yle Val Lys Leu Leu Ile

Tyr Tyr Thr Ser Thr Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp 85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys 100 105

<210> 53

50

<211> 119 <212> PRT

<213> Homo sapiens

<400> 53

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser 1 5 10

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn Tyr 20 25 30

Leu Tle Glu Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Lie 35 40

Gly Val Ile Tyr Pro Gly Ser Gly Gly Thr Asn Tyr Asn Glu Lys Phe 50 60

Lys Gly Arg Val Thr Leu Thr Val Asp Glu Ser Thr Asn Thr Ala Tyr 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Phe Cys 85 90 95

Ala Arg Arg Asp Gly Asn Tyr Gly Trp Phe Ala Tyr Trp Gly Gln Gly

Thr Leu Val Thr Val Ser Ser

<210> 54

<211> 119 <212> PRT

<213> Mus musculus

<400> 54 Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Gly Pro Gly Thr 1 5 10 15

Ser Val Arg Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn Tyr 20 . 25 Ser Gly Tyr Ala Phe 30

Leu Ile Glu Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile $35 \hspace{1cm} 40 \hspace{1cm} 45$

Gly Val Ile Tyr Pro Gly Ser Gly Gly Thr Asn Tyr Asn Glu Lys Phe 50 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr Thr Ala Tyr 65 70 70 80

Met Gln Leu Ser Ser Leu Thr Ser Asp Asp Ser Ala Val Tyr Phe Cys 85 90 95

Ala Arg Arg Asp Gly Asn Tyr Gly Trp Phe Ala Tyr Trp Gly Arg Gly 100 105 110

Thr Leu Val Thr Val Ser Ala 115

<210> 55

<211> 214 <212> PRT

<212> PRT <213> Homo sapiens

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Asn Asn Tyr 20 25 . 30

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Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro

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Pro Lys Pro Trp Ile Tyr Ala Thr Ser Asn Leu Ala Ser Gly Val Pro

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Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn 65 70 75

Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser 90 90 90 95

Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val $100 \,$ $105 \,$ $110 \,$

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Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val 65 70 80

Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln 95 95

His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro 100 105 110

Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn 115 120 125

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Glu Lys Thr Ser Asp Gln Ile His Phe Phe Phe Ala Lys Leu Asn Cys 145 150 155 160

Arg Leu Tyr Arg Lys Ala Asn Lys Ser Ser Lys Leu Val Ser Ala Asn 165 170 175

Arg Leu Phe Gly Asp Lys Ser Leu Thr Phe Asn Glu Thr Tyr Gln Asp 180 185 190

Ile Ser Glu Leu Val Tyr Gly Ala Lys Leu Gln Pro Leu Asp Pne Lys 195 200 205

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Lys Thr Glu Gly Arg Ile Thr Asp Val Ile Pro Ser Glu Ala Ile Asn 225 230 235 240

Trp Lys Ser Lys Phe Ser Pro Glu Asn Thr Arg Lys Glu Leu Phe Tyr 260 265 270

Lys Ala Asp Gly Glu Ser Cys Ser Ala Ser Met Met Tyr Gln Glu Gly 275 280 285

Lys Phe Arg Tyr Arg Arg Val Ala Glu Gly Thr Gln Val Leu Glu Leu 290 295 300

Pro Phe Lys Gly Asp Asp Ile Thr Met Val Leu Ile Leu Pro Lys Pro 305 310 315

Glu Lys Ser Leu Ala Lys Val Glu Lys Glu Leu Thr Pro Glu Val Leu 325 330 335

Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met 340 345 345

Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln 355 360 . 365

Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro 370 380

Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe 385 390 395

His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala 405 410

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<213> Homo sapiens

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Ser Thr Gly Phe Cys Pro Pro Leu Pro His Ser Gln Ala Asp Gln Tyr

Val Leu Ser Trp Asp Gln Gln Leu Asn Leu Ala Tyr Val Gly Ala Val

Pro His Arg Gly Ile Lys Gln Val Arg Thr His Trp Leu Leu Glu Leu 90 85

Val Thr Thr Arg Gly Ser Thr Gly Arg Gly Leu Ser Tyr Asn Phe Thr

100 105 110

His Leu Asp Gly Tyr Leu Asp Leu Leu Arg Glu Asn Gln Leu Leu Pro

115 120 125

Gly Phe Glu Leu Met Gly Ser Ala Ser Gly His Phe Thr Asp Phe Glu 130 135

Asp Lys Gln Gln Val Phe Glu Trp Lys Asp Leu Val Ser Ser Leu Ala 145 150 155 160

Arg Arg Tyr Ile Gly Arg Tyr Gly Leu Ala His Val Ser Lys Trp Asn 165 170 175

Phe Glu Thr Trp Asn Glu Pro Asp His His Asp Phe Asp Asn Val Ser 180 185

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Phe His Thr Pro Pro Arg Ser Pro Leu Ser Trp Gly Leu Leu Arg His 225 230 235

Cys His Asp Gly Thr Asn Phe Phe Thr Gly Glu Ala Gly Val Arg Leu 245 250 255

Asp Tyr Ile Ser Leu His Arg Lys Gly Ala Arg Ser Ser Ile Ser Ile 260 265

Leu Glu Glu Lys Val Val Ala Gln Gln Ile Arg Gln Leu Phe Pro 275 280 285

Lys Phe Ala Asp Thr Pro Ile Tyr Asn Asp Glu Ala Asp Pro Leu Val 290 295 300

Gly Trp Ser Leu Pro Gln Pro Trp Arg Ala Asp Val Thr Tyr Ala Ala 305 310315315

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Leu Ser Tyr His Pro His Pro Phe Ala Gln Arg Thr Leu Thr Ala Arg 355 360 365

Phe Gln Val Asn Asn Thr Arg Pro Pro His Val Gln Leu Leu Arg Lys 370 380

Pro Val Leu Thr Ala Met Gly Leu Leu Ala Leu Leu Asp Glu Glu Gln 385 390 400

Leu Trp Ala Glu Val Ser Gln Ala Gly Thr Val Leu Asp Ser Asn His 405 415

Thr Val Gly Val Leu Ala Ser Ala His Arg Pro Gln Gly Pro Ala Asp 420 425 430

Ala Trp Arg Ala Ala Val Leu Ile Tyr Ala Ser Asp Asp Thr Arg Ala 435 440 445

Eis Pro Asn Arg Ser Val Ala Val Thr Leu Arg Leu Arg Gly Val Pro 450 450

Pro Gly Pro Gly Leu Val Tyr Val Thr Arg Tyr Leu Asp Asn Gly Leu 465 470 475 480

Cys Ser Pro Asp Gly Glu Trp Arg Arg Leu Gly Arg Pro Val Phe Pro

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Ala Leu Arg Leu Pro Ser Leu Leu Leu Val His Val Cys Ala Arg Pro 530 535 540

Glu Lys Pro Pro Gly Gln Val Thr Arg Leu Arg Ala Leu Pro Leu Thr 545 550 550

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Cys Leu Trp Thr Tyr Glu Ile Gln Phe Ser Gln Asp Gly Lys Ala Tyr $580 \hspace{1.5cm} 585 \hspace{1.5cm} 585 \hspace{1.5cm} 590 \hspace{1.5cm}$

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Pro Asp Thr Gly Ala Val Ser Gly Ser Tyr Arg Val Arg Ala Leu Asp 610 615 620

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- <211> 429 <212> PRT
- <213> Homo sapiens

<400> 68

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Asp	Asn	Gly 35	Leu	Ala	Arg	Thr	Pro 40	Thr	Met	Gly	Trp	Leu 45	His	Trp	Glu	
Arg	Phe 50	Met	Сув	Asn	Leu	Asp 55	Cys'	Gln	Glu	Glu	Pro 60	Asp	Ser	Cys	Ile	
Ser 65	Glu	Lys	Leu	Phe	Met 70	Glu	Met	Ala	Glu	Leu 75	Met	Val	Ser	Glu	Gly 80	
Trp	Lys	Asp	Ala	Gly 85	Tyr	Glu	Tyr	Leu	Cys 90	Ile	Asp	Asp	Суз	Trp 95	Met	
Ala	Pro	Gln	Arg 100	Asp	Ser	Glu	Gly	Arg 105	Leu	Gln	Ala	Asp	Pro 110	Gln	Arg	
Phe	Pro	His 115	Gly	Ile	Arg	Gln	Leu 120	Ala	Asn	Tyr	Val	His 125	Ser	ГÀЗ	Gly	
Leu	Lys 130	Leu	Gly	Ile	Tyr	Ala 135	Asp	Val	Gly	Asn	Lys 140	Thr	Cys	Ala	Gly	
Phe 145	Pro	Gly	Ser	Phe	Gly 150	Tyr	Tyr	Asp	Ile	Asp 155	Ala	Gln	Thr	Phe	Ala 160	
_			Val	165					170					175.		
Leu	Glu	Asn	Leu 180	Ala	Asp	Gly	Tyr	Lys 185	His	Met	Ser	Leu	Ala 190	Leu	Asn	
Arg	Thr	Gly 195	Arg	Ser	Ile	Val	Tyr 200	Ser	Cys	Glu	Trp	Pro 205	Leu	Tyr	Met	
Trp	Pro 210	Phe	Gln	ĻУs	Pro	Asn 215	Tyr	Thr	Glu	Ile	Arg 220	Gln	Tyr	Cys	Asn	
His 225	Trp	Arg	Asn	Phe	Ala 230	Asp	Ile	Asp	Asp	Ser 235	Trp	Lys	Ser	Ile	Lys 240	
Ser	Ile	Leu	Asp	Trp 245	Thr	Ser	Phe	Asn	Gln 250	Glu	Arg	Ile	Val	Asp 255	Val	
Ala	Gly	Pro	Gly 260		Trp	Asn	Asp	Pro 265	Asp	Met	Leu	Val	11e 270	Gly	Asn	
Phe	Gly	Leu 275	Ser	Trp	Asn	Gln	Gln 280	Val	Thr	Gln	Met	Ala 285	Leu	Trp	Ala	
Ile	Met 290		Ala	Pro	Leu	Phe 295	Met	Ser	Asn	Asp	Ъеи 300	Arc	His	Ile	Ser	
Pro 305		Ala	Lys	Ala	Leu 310		Gln	Asp	Lys	Asp 315	Val	Ile	Ala	Ile	Asn 320	
Gln	Asp	Pro	Leu	Gly 325	Lys	Gln	Gly	Tyr	Gln 330	Leu	Arg	Glr	Gly	Asp 335	Asn	

Phe Glu Val Trp Glu Arg Pro Leu Ser Gly Leu Ala Trp Ala Val Ala 340 345 350

Met Ile Asn Arg Gln Glu Ile Gly Gly Pro Arg Ser Tyr Thr Ile Ala 355 360 365

Val Ala Ser Leu Gly Lys Gly Val Ala Cys Asn Pro Ala Cys Phe Ile 370 375 380

Thr Gln Leu Leu Pro Val Lys Arg Lys Leu Gly Phe Tyr Glu Trp Thr 385 390 395 400

Ser Arg Leu Arg Ser His Ile Asn Pro Thr Gly Thr Val Leu Leu Gln $405 \ \ \,$ 410 $\ \ \,$ 415

Leu Glu Asn Thr Met Gln Met Ser Leu Lys Asp Leu Leu
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<212> DNA

<213> Homo sapiens

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Glu Cys Thr Leu Gln Glu Asn Pro Phe Phe Ser Gln Pro Gly Ala Pro 35 40 45

Ile Leu Gln Cys Met Gly Cys Cys Phe Ser Arg Ala Tyr Pro Thr Pro 50 60

Leu Arg Ser Lys Lys Thr Met Leu Val Gln Lys Asn Val Thr Ser Glu 65 70 75 80

Ser Thr Cys Cys Val Ala Lys Ser Tyr Asn Arg Val Thr Val Met Gly 85 90 95

Gly Phe Lys Val Glu Asn His Thr Ala Cys His Cys Ser Thr Cys Tyr

Tyr His Lys Ser

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<211> 498 <212> DNA

<213> Homo sapiens

~400\ 71

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<400> 72

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Asn Ala Thr Leu Ala Val Glu Lys Glu Gly Cys Pro Val Cys Ile Thr 35 40 45

Val Asn Thr Thr Ile Cys Ala Gly Tyr Cys Pro Thr Met Thr Arg Val

50

Leu Gln Gly Val Leu Pro Ala Leu Pro Gln Val Val Cys Asn Tyr Arg

Asp Val Arg Phe Glu Ser Ile Arg Leu Pro Gly Cys Pro Arg Gly Val

Asn Pro Val Val Ser Tyr Ala Val Ala Leu Ser Cys Gln Cys Ala Leu 105

Cys Arg Arg Ser Thr Thr Asp Cys Gly Gly Pro Lys Asp His Pro Leu

Thr Cys Asp Asp Pro Arg Phe Gln Asp Ser Ser Ser Lys Ala Pro

Pro Pro Ser Leu Pro Ser Pro Ser Arg Leu Pro Gly Pro Ser Asp Thr 155 145

Pro Ile Leu Pro Gln 165

<210> 73

<211> 165 <212> PRT

<213> Homo sapiens

<400> 73

Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu

Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His

Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe

Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp

Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu

Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp

Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu

Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala

Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val 130

Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala 155

Cys Arg Thr Gly Asp 165

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<213> Homo sapiens

<400> 74

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<212> PRT

<213> Homo sapiens

<400> 75

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Ser Pro Val Gly Ser Leu Gly Cys Asp Leu Pro Gln Asn His Gly Leu 20

Leu Ser Arg Asn Thr Leu Val Leu Leu His Gln Met Arg Arg Ile Ser

Pro Phe Leu Cys Leu Lys Asp Arg Arg Asp Phe Arg Phe Pro Gln Glu 60

Met Val Lys Gly Ser Gln Leu Gln Lys Ala His Val Met Ser Val Leu 65

His Glu Met Leu Gln Gln Ile Phe Ser Leu Phe His Thr Glu Arg Ser 85 90

PCT/US2004/011494 WO 2004/099231 Ser Ala Ala Trp Asn Met Thr Leu Leu Asp Gln Leu His Thr Gly Leu

His Gln Gln Leu Gln His Leu Glu Thr Cys Leu Leu Gln Val Val Gly 120

Glu Gly Glu Ser Ala Gly Ala Ile Ser Ser Pro Ala Leu Thr Leu Arg 135

Arg Tyr Phe Gln Gly Ile Arg Val Tyr Leu Lys Glu Lys Lys Tyr Ser 145

Asp Cys Ala Trp Glu Val Val Arg Met Glu Ile Met Lys Ser Leu Phe

Leu Ser Thr Asn Met Gln Glu Arg Leu Arg Ser Lys Asp Arg Asp Leu 185

Gly Ser Ser 195

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